UNIVERSITY
OF MICHIGAN
JUN 1 3 1951
MEDICAL
LIBRARY

VOLUME 44 NUMBER 5 MAY 1951

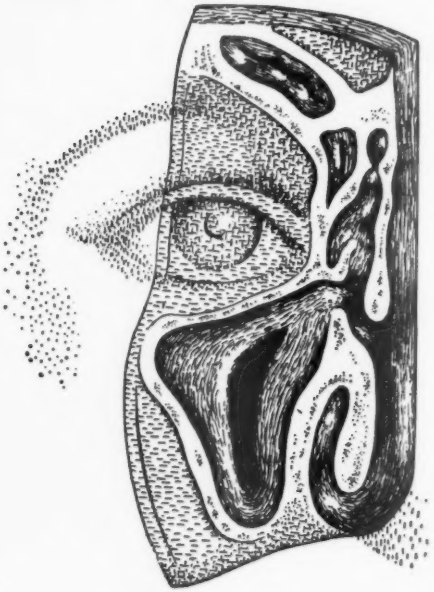
PROCEEDINGS

of the

ROYAL SOCIETY OF MEDICINE

Published for
THE ROYAL SOCIETY OF MEDICINE, 1 WIMPOLE STREET, LONDON, W1
by
H. K. LEWIS & Co. LTD., 136 GOWER STREET, LONDON, W.C.1
In U.S.A., GRUNE & STRATTON, INC., 381, FOURTH AVENUE, NEW YORK CITY
Monthly, 10s. 6d. net. Annual Subscription, £6 6s. in the British Commonwealth, $19.00 in the U.S.A.

All rights reserved



anti-histamine

and

nasal

decongestant

FORMULA

'Benadryl' (Diphenhydramine Hydrochloride)	0·1 per cent.
Ephedrine Hydrochlorde	1 per cent.
Chloretone	0·5 per cent.
Menthol	0·05 per cent.
Aqueous dextrose base	q.s.

'Bena-Fedrin'

Contains the anti-histamine agent 'Benadryl' and the vaso-constrictor ephedrine, is an isotonic aqueous dextrose vehicle approximating in *p*H to that of the normal nasal secretions. In addition to being miscible with mucous discharge and reaching membrane surfaces rapidly, it is relatively non-irritating.

'Bena-Fedrin' is intended for use in the treatment of congestion associated with allergic rhinitis, hay-fever and other pollen allergies, acute rhinitis, acute rhino-sinusitis, etc.

In bottles of 1 fl. oz. and 16 fl. oz. *Subject to Schedule 4 Poisons Regulations.*

PARKE, DAVIS & COMPANY

Inc. U.S.A., Liability Ltd

HOUNSLOW, MIDDLESEX

Section of Psychiatry

President—E. O. Lewis, D.Sc., M.R.C.S.

[*January* 9, 1951]

Studies in the Physiology of Awareness: Oximetric Evidence of the Role of Anoxia in Certain Psychiatric States [1]

By J. W. Lovett Doust, B.Sc., M.B., M.R.C.P.
University of London Institute of Psychiatry, Maudsley Hospital

The relationship between oxygen metabolism and psychiatric disorder has been explored by many workers in the past and from several differing points of view. The pioneer observations of Paul Bert, Mosso, Barcroft, Haldane, McFarland, Armstrong, Gellhorn and others have been reviewed by van Liere (1942) and by Hoskins (1946), the latter considering the symptoms produced by defective oxygen assimilation to be "at least of the same general order" as those of schizophrenia. Mental changes accompanying the anoxia induced by anæsthetic agents have similarly been discussed by Lucas (1950). That there is an intimate connexion between the psychiatric symptomatology appearing in states of anoxia and that observed in syndromes of so-called idiopathic mental disorders seems to be unquestioned. Between the normal personality not so influenced, and the complete unconsciousness or death following the induction of fulminating anoxia, appears to exist a more chronically anoxic borderland wherein may be found many of the representative syndromes of mental disturbance.

"An intimate connexion" we have called this relationship between anoxia and the phenomenology of psychiatric states; it is a connexion so intimate that the induction of the one leads to the appearance of the other, and vice versa. Yet the data in existence for the occurrence of anoxia in cases of mental disturbance have seldom been found on direct examination: they have been in the past in the nature of epiphenomena and as such, if overwhelming in their abundance, only circumstantial in their application. Perhaps the failure of previous investigators to demonstrate an anoxæmia in, e.g., constitutional schizophrenia, has been the necessity they have had of employing such relatively time-consuming techniques on *in vitro* blood obtained by traumatic arterial punctures from grossly large blood vessels. Oximetric methods are open to none of these objections although they are by no means free from certain other criticisms.

An oximeter is an instrument which will measure, in a matter of a few seconds and with minimal co-operation from the subject, the oxygen saturation of the blood in minute vessels *in vivo*, without acupuncture and without trauma. All oximeters depend upon the fact that the transmission of light by oxyhæmoglobin differs from its transmission by reduced hæmoglobin. This difference is capable of quantitative interpretation and, by standardization, of being expressed in terms of percentage saturation of hæmoglobin with oxygen.

Two types of oximeter have been used in the investigation reported here. The first employs a principle initially noted by Vierordt in 1878 and rediscovered by Ray in 1946 who developed it into a method for measuring what he termed the "Reduction Time" of the blood of the skin vessels of the dorsum of the hand. Ray's technique has been further modified and, since the main instrument used is a pocket spectroscope, we have called this a method of *spectroscopic oximetry*. Essentially the method depends upon the fact that the spectroscopic absorption bands of oxyhæmoglobin disappear following occlusion of the peripheral circulation in a number of seconds which bears a constant relationship to the oxygen saturation of the blood in the vessels examined. On a large number of healthy subjects, Ray found the mean Reduction Time to be 37·7 seconds and concurrent estimations of the alveolar oxygen tension on the same subjects yielded a correlation coefficient between the two of + 0·87, indicating a very close relationship between these variables. The modified method used in the present study employed the skin of the finger nail fold

[1] This work was done during the tenure of a Nuffield Foundation Medical Fellowship in London and New York.

as the site of examination and yielded a mean Reduction Time on 112 healthy subjects of 41·143 seconds, with a Standard Deviation of 8·904—a figure closely approximating to that of Ray. Spectroscopic oximetry is no more disturbing to the patient than is the taking of his blood pressure; estimations occupy less than a minute; they are infinitely reproducible; they have a high reliability and a reasonable validity. The method is discontinuous and applicable to any suitable area of skin.

The second technique employed was that of *photo-electric oximetry*, using the instrument designed by Millikan in 1942. Here the site of estimation is the blood of the pinna of the ear. Analysis is made continuously, the constant fluctuation in oxyhæmoglobin content of arterial blood in the heat-dilated vessels being picked up by means of a presensitized barrier-type photo-cell energized by a constant current lamp, the whole unit being enclosed in a compact earpiece. The circuit is compensated for different ear thicknesses and the changes in potential are recorded continuously by a galvanometer against a scale from which percentage oxygen saturation can be read directly. Accuracy against arterial puncture and subsequent Van Slyke gasometric analysis has been found to lie within 5% in the range 75–100% oxygen saturation. Individual pre-standardization of the instrument, by flooding the subject's circulation with oxygen, is necessary before the galvanometer reading can be accepted with confidence. A series of 285 simultaneous observations on a number of subjects was made using these two methods of spectroscopic and photo-electric oximetry: they yielded a correlation coefficient of + 0·91 and a convenient regression equation for the calculation of percentage arterial oxygen saturation values from Reduction Time seconds.

The present investigation is based on an oximetric study of 146 healthy control subjects, 75 psychoneurotic patients, 22 patients with character disorders, 26 cases of depression, 87 patients with schizophrenia and 13 patients with various neurological conditions—a total of 369 subjects in all As the results obtained have been analysed statistically and are being reported elsewhere, I shall use protocol illustrations here, such examples being typical of responses within their individual categories.

Results in Healthy Control Subjects

The critical range of arterial saturation levels in health is usually given as lying between 92–93 and 98% oxygen. Our findings confirm these figures and show them also to hold over protracted periods of examination. Fig. 1 is an example of the results of continuous oximetry in a healthy subject, fluctuations about the baseline being of the order of 1–2%. Such fluctuations were at first thought to be due to instrumental discrepancies but later situational analysis showed them to be meaningful in terms of variations in awareness and states of tension; in terms, in fact, of constantly fluctuating thresholds of consciousness. This inference is exemplified in Fig. 2, the oximetric analysis of another subject, investigated

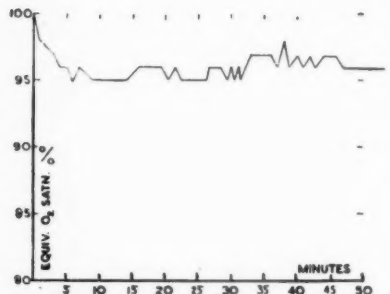


Fig. 1.—Healthy male, aged 30. Ordinates for this and subsequent charts: per cent arterial oxygen saturation; abscissa: time in mins. Note the rise in baseline values by approx. 1% with increased attention.

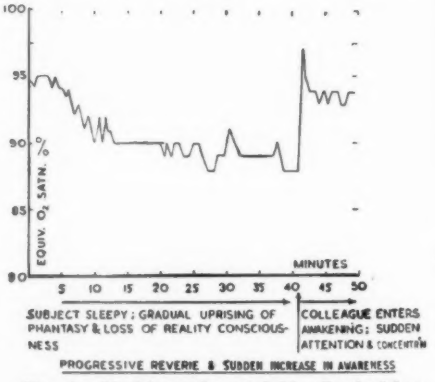


Fig. 2.—Healthy male, aged 35. Gradual loss of attention as phantasy and emotional tensions arise. Subject sinks into light sleep and is suddenly awakened.

this time following a heavy midday meal. He felt tired, his attention began to wander, he fell into a brown study and allowed his imagination to run riot. The reverie merged into a state of light sleep (O_2 = 89–90%) from which sudden awakening ensued as a colleague

burst into the room and commenced an animated conversation (O_2 = 94–97%). An oximetric study of natural nocturnal sleep in a group of 12 subjects (Lovett Doust and Schneider, 1951) revealed the same tendencies, oxygen levels down to 87% saturation being reached in deep sleep.

The oximetric responses to a variety of different stresses were investigated in the control group. Fig. 3 shows the effect of repeated blood-pressure recordings and also that of a period of exercise in which the subject's arms moved against resistance to the point of fatigue. Fig. 4 illustrates the effect of a massive intake of alcohol followed over a prolonged

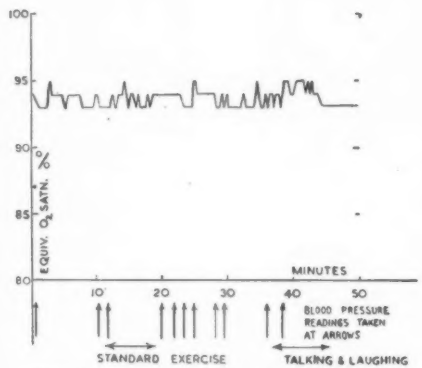


FIG. 3. — Healthy male, aged 32. Minor stresses. Note complete and rapid homeostatic adjustment oximetrically to such stress.

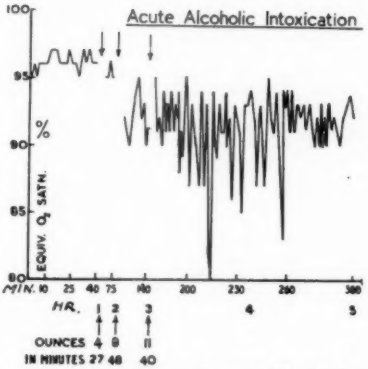


FIG. 4.—Healthy male, aged 32. Major stress. Here homeostasis is sorely taxed and oximetric adjustments are slow and ill-sustained. Whisky (100 proof) taken at times marked with arrows.

time period. The subject of this experiment became very intoxicated, at the height of which he was stuporose. Successive psychiatric examinations during the course of the intoxication revealed that his mental state deteriorated in step with the progressive intensity of, and decompensation to, the anoxæmia. Although alcohol is usually regarded as an agent evoking the histotoxic type of anoxia, the extreme fluctuations produced in the arterial oxygen saturation levels would seem to suggest additional cardio-respiratory effects of this intoxicant and impairment of the normally rapid homeostatic adjustments.

Very similar to the effects of alcohol were the results of a rather heroic experiment designed to assess psychiatrically the effects of anoxic anoxia. Sleep had been noted, as we have said, to be accompanied by oxygen saturation levels around 87% in its deepest plane: Oxygen-nitrogen mixtures were accordingly breathed to depress, under oximetric control, a normal baseline of 94–95% oxygen down to 86–88% saturation. We wished to discover, in other words, the psychiatric effects of being awake under the oximetric conditions of deep sleep. Briefly the findings were as follows:

Case 1.—Healthy male, aged 35. *After five minutes* at 85–89% oxygen sat. the subject reported that he felt sleepy; *after fifteen minutes* his vision was blurred and he had a frontal headache; *after thirty minutes* he showed flushing of the face with coldness of the extremities, he was grimacing and laughing inappropriately; *after sixty minutes* he was complaining of dizziness and feelings of depersonalization; echolalia, rhyming, punning and tangential associations to attempted conversation were noted; *after two hours*, he showed lability of mood, tension, a phasic "dipping of consciousness" similar to that reported in accidental carbon monoxide poisoning, and babbling, slurred speech; *after three hours*, euphoria was marked but alternated with periods of extreme anxiety, insight was waning, perceptual data seemed unreal to him, orientation for time became muddled but that for other modalities remained clear; intermittent waxy flexibility, cataplexy and silly laughter were present; *after four hours*, he reported immense weakness, anergy and fatigue, everything around him appeared "unreal and dream-like", there was a "hissing" in his ears; clinically he showed echopraxia, surly irritability and resentment, projected anxiety and paranoid ideation and there were marked fluctuations in attention and awareness; *after six hours*, the subject was yawning, complaining that "everything seems remote," "my thoughts don't seem to belong to me", he was catatonically stuporose, negativism and perseveration were marked and affect and empathy grossly diminished. *That night* the subject slept fitfully, his baseline oxygen saturation levels the following day running around 91–93% and accompanying a sense of great fatigue to minimal effort but the *third day* he was himself again and had regained his former saturation baseline of 94–95% oxygen.

Psychoneurosis

In contrast to the negligible baseline fluctuations noted in continuous oximetry in healthy subjects under the impact of minor stress, neurotics showed wide variations in their responses. Fig. 5 is the record of a young law student suffering from a chronic anxiety state for which

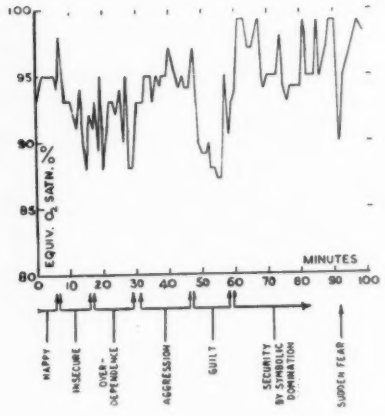


FIG. 5.—Neurotic male, aged 25. Note extreme instability of baseline even when he feels secure and the temporal identity of states of emotional tension with appearance of anoxia (*Case* 2).

he was receiving psychotherapy. A directive psychiatric interview (*Case* 2) with concurrent oximetry was undertaken, stress situations developing as a result of a discussion of the patient's feelings regarding certain emotionally charged events in his life history.

Case 2.—Male, aged 25. "Happy" (O_2 = 93–98%). He says he is much improved as a result of previous interviews. "Insecure" (O_2 = 97→93%). Discussion of his attempts to prove himself superior revealed (O_2 94→88%) his efforts to be founded on a realization of his own inferiority feelings. "Overdependence". His mother babies him (O_2 95→88%) and he cannot leave her; he always breaks down when he tries to leave home. He wonders: is death (O_2 95→88%) a way out? "Aggression." He is ambivalent towards his big, aggressive, forthright and dominating uncle (O_2 = 93–97%). He desires to be masterful like this uncle. "Guilt." Mention of his father makes him depressed (O_2 97→87%). He feels guilty about his own aggressive impulses. "Security by symbolic domination." He can achieve security (O_2 87→95%) by reconciliation with the Church and by finding fame in his profession. "Sudden fear" (O_2 98→90%). "But I am still afraid of my uncle."

Schizophrenia

A cross-sectional oximetric study of "constitutional" schizophrenic patients demonstrated an anoxæmia consistently below 92% to be characteristic of cases of dementia præcox simplex, catatonic schizophrenia and hebephrenia. Furthermore, neither age nor sex, duration of illness nor diagnostic subtype appeared to play any part in their oximetric differentiation. Fig. 6 illustrates the result of a psychiatric interview with a florid hebephrenic and Fig. 7 a similar interview with a paranoid schizophrenic. Both patients showed reasonable empathy and *rapport* after oxygen inhalation while the oxygen saturation levels were relatively normal, but schizophreniform phenomena became increasingly prominent as the baseline anoxia appeared. The interview with the hebephrenic is briefly outlined below: concomitance of intensity of anoxia and extent of personality fragmentation is particularly well shown (Fig. 6, *Case* 3).

Case 3.—Male, aged 23. *At* 93% *oxygen*, he was saying: "I am in Hospital for help." *At* 88% *oxygen*, he was producing word salads, rhyming, punning, with thought blocking and neologisms: "I am two years post-mature, but one must fight to keep alive. Unless it is quoted on paper. Am I right? Its a girl. In 'metaphoca'. I was going to be a girl but my mother was the U.S. Army. I, 'eye'. I never wanted to kill him." *At* 87% *oxygen*: "I saw a 'thurblack', a shadow cast. There's a new language, shall I cancel the spell? But for '4' focus. For 4. I utter words to recall past mental focus. Utter core. The whole. Past ages took my soul. It was because of one tooth. Green tear drops are but a shadow cast." *At* 86% *oxygen*, he was perseverating: "Smoke. Smoke. The testicle teeth are a dead weight." *At* 85% *oxygen*, he was uttering isolated words: "'Dreason.' Woman. Mother." *At* 84% *oxygen*, the one word: "Coma." *At* 87% *oxygen* again, he said: "I am now almost out of coma, save for some extraction."

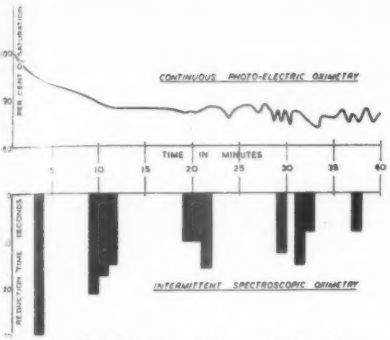


FIG. 6.—Hebephrenic male, aged 23. At zero minutes the patient ceased oxygen inhalation. Note progressive fall in oxygen levels to a base-line of approx. 86% and concurrence of the two oximetric methods (*Case* 3).

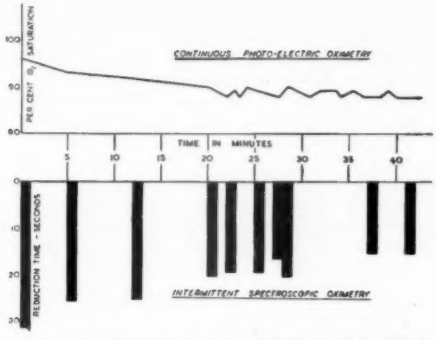


FIG. 7.—Paranoid schizophrenic male, aged 34. Interview stress was sufficient to unmask a consistent anoxæmia after fifteen minutes.

Fig. 8 records a similar response oximetrically in a destructive and unpredictable schizophrenic patient and contrasts with it the effect of deep insulin coma therapy. Concomitantly with the improved blood oxygen saturation levels, the patient showed a marked change in his mental state emphasizing physical complaints and speaking of hallucinatory experiences in the past tense.

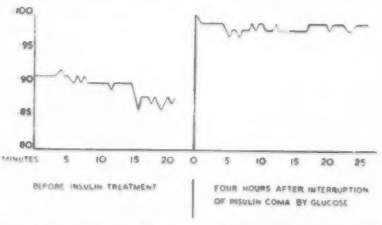


FIG. 8.—Schizophrenic male, aged 36. The oxæmia following insulin therapy is running at pathologically high levels and the patient's mental state, although greatly changed, was by no means normal.

Interview: Suspicious-thought disorder-hallucinations.

Anergy and multifarious physical complaints—empathy sustained.

DISCUSSION AND CONCLUSIONS

It obviously cannot be maintained that these results directly represent oxygen saturation levels in cerebral vessels since they were obtained peripherally. They do, however, suggest that organismic effects are occurring both from the concordance of values in the two widely separated sites of examination and from the mental changes accompanying the oximetric fluctuations. It is a task for the future to apply suitably modified oximetric techniques to the study of the blood in vessels, perhaps, of the exposed brain during neurological operations.

What would appear to emerge, from the use of oximetric techniques, is that a common factor runs like a thread through the constantly fluctuating patterns of awareness seen in normal life; in the ever present minor stresses which make up day-to-day existence; in the prototypes of major stress demands and the response of our homeostatic mechanisms to those demands; in the periodicities like sleep which impinge in phasic fashion on our individual pattern of consciousness. This common factor, or thread, is the organism's unique efforts to maintain a level of arterial blood oxygen saturation which represents for him an adequate balance of normal functioning potential and at the same time lies within the critical range of his brother's normal needs.

We would also suggest that an individual's relative success in the maintenance of such a homeostatic equilibrium with respect to oxygen saturation levels is a function as much as anything of the emotional stability his personality represents—emotionally unstable individuals, such as those with psychoneurosis, being unable to maintain the same sort of

relatively stable baseline in the face of life situational stress and responding with wide swings well outside the critical range of functional normality.

Finally we have seen that schizophrenic individuals who, for one reason or another, have more or less permanently been unable to sustain blood-oxygen saturation levels consistent with the normal range of consciousness, represent a pattern of awareness very similar to that experienced during life at high altitudes or under any other condition of defective oxygen assimilation. Many such patients, by voluntary empathic effort, can initially give the appearance of relatively normal awareness but the pall of anoxia soon falls on this, their arterial oxygen drops to the levels of sleep and their mental state conforms once more to Jung's remark about the schizophrenic—that he is a "dreamer in a world awake". And we have seen how the schizophrenic process may be reversed by insulin coma; we might have added that such apparent reversal only occurs, in our experience, when the delayed effect of this coma is to raise the oxygen saturation levels.

Consciousness at one level or another is a dimension of life for the human personality and to the deviations from its thresholds can be attributed much of the phenomenology we see in psychiatry. If emotional tension be created by a conflict of desires denied expression, awareness falls away and a reality potential tends to be replaced by one of phantasy. But at the same time that consciousness is dimmed, anoxia appears; conversely, when empathy and attention raise the thresholds of anoxia, conscious awareness increases and the oxygen saturation levels parallel its rise. And aside from all this is the significant fact that, with the induction of experimental anoxic anoxia and in step with the consequent fall in arterial oxygen saturation, there follows the sequence of diminishing awareness, uprising of emotional tension and instability, effective lability and that fragmented, chaotic, irresponsible, dream-like pattern of consciousness which is schizophreniform in quality when wakefulness is forced upon him who experiences it, yet whose *alter ego* is natural sleep.

"Consciousness", says Schroedinger in echoing the Orientals, "is a singular of which the plural is unknown". It would appear to me that the arterial oxygen saturation levels of the blood are merely a series of different aspects of consciousness, another way of looking at the same thing.

REFERENCES

Hoskins, R. G. (1946) The Biology of Schizophrenia. London.

Van Liere, E. J. (1942) Anoxia: Its Effect on the Body. Chicago, Ill.

Lovett Doust, J. W., and Schneider, R. A. (1951) Anoxia and the Levels of Sleep. London. (In press.)

Lucas, B. G. B. (1950) *Proc. R. Soc. Med.*, **43**, 606.

Millikan, G. A. (1942) *Rev. Sci. Instrum.*, **13**, 434.

Ray, G. B. (1946) *Amer. J. Physiol.*, **147**, 622.

Section of Laryngology

President—A. M. ZAMORA, M.Ch., F.R.C.S.

[*December* 1, 1950]

The Approach to the Nasopharynx

By C. P. WILSON, C.V.O., F.R.C.S.

THE nasopharynx with its adjacent basi-sphenoidal and posterior ethmoidal regions presents one of the most difficult problems in our specialty, from the point of view of both diagnosis and treatment.

The clinical examination of the nasopharynx is the most difficult of all our various methods of examination and even if a satisfactory view is obtained the interpretation of what is seen may still present great difficulty. Evidence of this is to be found in the variety of the methods used—digital examination, the use of some form of direct speculum, and the use of a postnasal mirror with possibly some form of palatal retractor.

With the invention of the nasopharyngoscope it was hoped that the problem of the difficulty of inspection was solved, but in my experience this instrument has proved rather disappointing in use and in my own practice it is limited to ensuring that a eustachian catheter is really in correct position before passing a bougie.

Even when a correct diagnosis has been made the problem of treatment still remains and the rather indifferent results of the surgical treatment of such conditions as atresia of the choana, nasopharyngeal fibroma or carcinoma are testimony to the difficulty of access.

This problem of access is no new one and even as long ago as 1853 Michaux described for this purpose an approach by lateral rhinotomy and since that time many varieties of operation designed to improve the access have been described. Many of these operations have been designed more especially to deal with tumours of the pituitary gland and others for dealing with tumours of the maxillo-ethmoidal region but all are alike in aiming to improve the approach to this almost inaccessible area.

There have been three main avenues of approach: (*a*) through the nose ; (*b*) through the upper jaw; and (*c*) through the mouth.

(*a*) A direct approach to the nasopharynx may be made through the external nares after shrinking the mucosa with cocaine and adrenaline. More room may be obtained by fracturing the inferior or middle turbinates outwards or by excising portions of them and by these means small growths may be partially or completely excised and an approach made to the sphenoidal sinus.

The application of this method is of course limited by the size of the growth; extensions of the method to obtain better access have been suggested by many surgeons.

All involve separation of the soft tissue of the nose from the underlying bone followed by removal of the septum and other portions of the inside of the nose or of the lateral nasal wall.

Rouge and Halstead described operations in which a sublabial incision was employed stretching from one canine fossa to the other. The lip was everted, and

the alæ nasi elevated from the bone and the nasal septum divided or partially removed.

Others such as Langenbeck and Ollier have used incisions on the face with the turning aside of part or the whole of the soft tissues.

The disadvantage of these facial methods of approach is that they are all associated with considerable post-operative scarring and deformity and although they give a good access to the front of the nose and the sphenoidal area they give a very poor approach to the nasopharynx, and are now obsolete.

(*b*) Many methods of approach through the upper jaw have been described, but these can be grouped into two main classes according to whether the incision is made through the face or through the alveolar sulcus.

Langenbeck's operation of turning the nose laterally was modified by Eve and later by Watson-Cheyne using a partial excision of the upper jaw but the best known of these methods is Moure's lateral rhinotomy and this is still in use for major operations on the upper jaw.

The incision may be extended by dividing the lip in the middle line so as to turn back the whole of the cheek as described by Weber. The only useful sublabial approach is Denkers' extended operation in which the anterior wall of the maxilla, portions of the nasal bones and the frontal process of the maxilla are removed and also the antro-nasal wall.

None of these incisions is of much value as an approach to the nasopharynx because the line of approach is directed too high, as in the operations through the nose already mentioned.

(*c*) Approaches through the mouth and palate have mainly aimed at an antero-posterior incision of the soft and hard palate and have been described by Doyle, Moure, Delia, Escat and Nélaton.

Simple median incision of the soft palate without interference with the hard palate gives a most unsatisfactory exposure and is rarely worth while.

A straight incision commencing behind the alveolus but stopping short at the base of the uvula may be used and the under surface of the hard palate exposed. Portions of this and of the posterior part of the nasal septum may be removed; this incision gives a very adequate exposure of the region of the base of the nasal septum.

This approach is in fact the only method which I have so far mentioned which is of any real value. It is useful for conditions in the neighbourhood of the posterior border of the septum but it has several disadvantages, one of which is the difficulty of retraction of the flaps, while the exposure of the nasopharynx itself is not very good.

Two or three years ago I conceived the idea of making a transverse incision between the hard and the soft palate and then pushing the whole soft palate backwards. This concept I put into practice on a patient with a mixed salivary tumour bulging into the lateral nasopharyngeal wall and causing a complete nasal obstruction on the right side.

The operation was completely successful but only after I had extended the incision downwards to the outer side of the tonsillar fossa. I was surprised by the ease with which the palate was subsequently sutured and still more surprised by the complete absence of any post-operative disability. This success encouraged me to use this approach for other conditions of the nasopharynx and I have been most gratified by the exposure which it provides.

The position of the patient may be sitting up as in a septum or antral operation but with the mouth widely opened with a Boyle-Davis gag or in a young person with a very mobile neck the common tonsil position with the head hyper-extended. Intratracheal anæsthesia is used with a tube passed through the mouth or through the nose if the lesion is unilateral and the top of the larynx is occluded by a pack.

The tonsil position is not suitable for adults as the head cannot be sufficiently hyper-extended.

The area of the junction of the hard and soft palate is infiltrated with novocain and adrenaline and also the area between the tonsils and the pterygo-mandibular raphe.

The incision starts as a transverse one just in front of the posterior border of the hard palate and somewhat convex forwards. The edge of the bone can be identified accurately by puncturing with a needle. The incision goes right down to bone and the mucosa is separated backwards with a sharp raspatory until the edge is reached. The posterior spine of the hard palate is then removed with a gouge or chisel and the nasopharynx opened by dividing the upper surface of the soft palate at its junction with the hard palate.

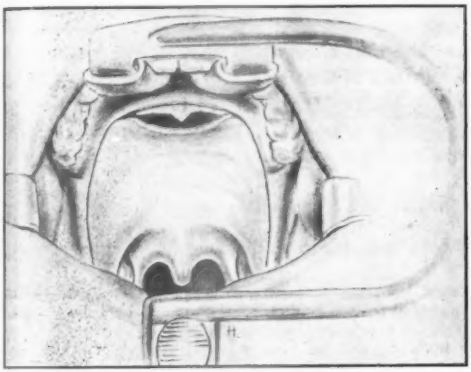


FIG. 1.

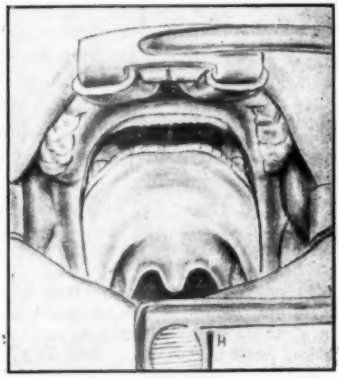


FIG. 2.

FIG. 3.

FIG. 1.—The line of the incision. The transverse part has gone down to bone which has been exposed and the nasopharynx opened by division of the mucosa of the upper surface of the palate at the edge of the bone.

FIG. 2.—The posterior spine of the hard palate has been removed and the incision extended laterally. The hamulus of the internal pterygoid plate and the tendons of the tensor palati muscle are just appearing at the extreme edge of the incision.

FIG. 3.—The incision has been completed and the whole soft palate pushed downwards and backwards. The posterior border of the nasal septum, the fossæ of Rosenmüller and the eustachian cushions and orifices are all clearly seen.

The incision is extended laterally until the pterygo-mandibular raphe is reached and then proceeds downwards along this ligament for as far as may be desired.

The hamulus of the internal pterygoid plate is identified by the finger and the tendon of the tensor palati muscle is seen passing across it. The tendon of the tensor palati muscle is divided just medial to the hamulus. When this has been done the soft palate can be retracted backwards using a right-angled retractor with a long handle and the mucous membrane of the lateral nasopharyngeal wall divided as far

as it is desired. The retractor can now be discarded as the soft palate can be pushed downwards and backwards until it is lying in contact with the epilaryngeal pack.

The bleeding is not very severe and is mostly from vessels passing backwards from the posterior palatine artery.

When the palate has been pushed back a most satisfactory view of the nasopharynx is obtained. The posterior border of the septum, the posterior ends of the turbinates, the fossæ of Rosenmüller and the eustachian orifices are easily seen.

After operation the soft palate is replaced and sutured by 3 or 5 sutures to the mucosa of the hard palate. No attempt is made to suture the upper surface and no attempt is made to close the lateral parts of the incision which do not gape.

There is no special post-operative treatment and there is practically no post-operative discomfort or disability. The patient can talk or swallow quite normally and has no pain.

It is an operation that offers a means of approach to the nasopharynx far superior to any previously described.

By extending the incision forwards in the mid-line lateral flaps of the mucosa of hard palate can be dissected up and a portion of the hard palate removed.

If this is done a submucous resection of the posterior part of the septum may be carried out and the whole of the basisphenoid exposed. This might prove a useful means of access to the pituitary region.

Mr. J. C. Hogg: The postnasal space has remained one of the most inaccessible regions for direct surgical treatment. The various lines of approach employed by past generations of surgeons, which the opener of this discussion has so ably reviewed, bear witness to the difficulty which this subject has always presented.

From time to time, transpalatal operations on the posterior choanæ have been described in the literature, and in 1945 Ruddy described an operation for the treatment of congenital choanal atresia in which he used a palatal approach. He made a curved incision across the palate starting internal to the posterior palatine artery, and carried his incision across the hard palate to the other side, anterior to the attachment of the soft palate. He also gave an interesting review of transpalatal surgery for this condition up to that date.

Being disappointed by the access obtained after vertical splitting of the soft palate in the mid-line, as well as by the occasional failure of union of the flaps, perusal of Ruddy's article suggested to me that perhaps a more extensive detachment of the palate might be employed with advantage in the surgical treatment of some post-nasal diseases. Mr. C. P. Wilson had already been employing the technique of extended detachment of the soft palate with success in a variety of conditions, and when I was confronted last year with a mixed salivary tumour occluding both choanæ, he very kindly put his experience at my disposal. In this case, as the tumour was large, the hamulus was detached from

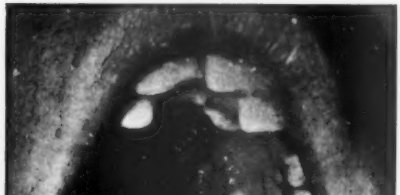


FIG. 1.—Shows healing palatal incision extending laterally downwards behind the alveolus.

FIG. 2.—Same case showing high narrow palatal arch giving pointed appearance to the centre of the incision.

the pterygoid plate on one side to give better access. The palatal incision healed by first intention and no post-operative disability could be detected.

Both my other 2 cases were examples of congenital choanal atresia. In one case the atresia was bilateral in a girl of 19. As seen in Figs. 1 and 2 she has a very high and narrow arch to her palate so that once again the hamulus was detached and the incision was extended downwards along the pterygo-mandibular raphe. In my view, the more limited incision advocated by Ruddy (1945), Dolowitz and Holley (1949) and others, would not have provided the requisite exposure in this instance.

In my last case the choanal atresia was masked by extensive and massive nasal adhesions on the right side, following a Caldwell-Luc operation performed at another hospital eight years previously. At first an effort was made to divide these adhesions, but it was then realized that there was a bony choanal atresia. A transpalatal operation was carried out for the removal of the bony obstruction. She now has a patent airway, although she still has some adhesions between the upper part of the nasal septum and the lateral nasal wall.

There are some practical points which I have learnt about this operation. I have on all three occasions used the right lateral position recommended years ago by Sir Henry Butlin for the tonsil operation. This allows the surgeon to sit comfortably on the right side of the table, while at the same time it provides sufficient head extension for visualizing the operative field. If a nostril is available, continuous suction with a catheter passed through the nose is time saving and frees the assistant's hands. In making the incision through the palate it is important to avoid the main anterior branch of the posterior palatine vessels, as otherwise bleeding may be profuse and difficult to control. The small posterior twigs have been easily picked up with forceps and controlled by diathermy coagulation. Inspection of the operative field is helped by the use of a mirror, particularly where there is choanal obstruction. This mirror also helps to push the detached palate out of the way. Re-suturing the palate is not attended by any special difficulties.

In the third case a stitch gave way, with the formation of a perforation near the mid-line. This, however, closed spontaneously without the need for any prosthesis.

None of the cases had any difficulty in swallowing or talking, and all three have retained their normal palatal function.

I would not hesitate to use this approach for any future cases of this nature.

REFERENCES

DOLOWITZ, D. A., and HOLLEY, E. B. (1949) *Arch. Otolaryng.*, **49**, 587.
RUDDY, L. W. (1945) *Arch. Otolaryng.*, **41**, 432.

The President said that in their new approach to this difficult area Mr. Wilson and Mr. Hogg had definitely established that the transverse incision was to be preferred to the longitudinal variety. It was strange that this idea had not been thought of before, it was so simple. He himself had found inconvenience and difficulty in using the longitudinal incision.

Mr. E. D. D. Davis said that for many years he had been considering this question of a better approach to the nasopharynx and it had not occurred to him to make a transverse incision across the palate. Mr. Wilson was the first to demonstrate it. He had watched Mr. Wilson operate on 3 cases and he had seen the patients afterwards. The exposure was excellent. There was little difficulty in the operation and there was practically no discomfort afterwards, the incision healed within a week and the patient was out of hospital in ten days.

He had tried all the other operations which Mr. Wilson mentioned and found them to be unsatisfactory and they caused considerable damage. The extension of the incision on to the fauces just above the tonsil gave an easier retraction and the bleeding could be easily controlled. The hamular process was felt with the finger. The tensor palati tendon was divided almost without knowing it. During an operation for the removal of bleeding fibroma of puberty the transverse incision gave an excellent exposure.

Mr. R. R. Simpson said that he had carried out this operation three times in the last two years since Mr. Wilson had told him about it. One part of it which had impressed him tremendously was the direct view one obtained of the orifice and the anterior border of the eustachian tube. This was quite striking, it was so easy, one could look straight into the eustachian tube. The last case he did was of a woman with a suspicious small swelling in front of the eustachian tube. Biopsy through the nose gave a doubtful answer but a shortened version of the transverse incision allowed him to see the eustachian tube and the swelling in front of it and that enabled him to make up his mind that it did not look benign. A biopsy from the centre of the mass showed it to be a chondrosarcoma. The incision had the tremendous advantage that it would give an extraordinarily good view, better than could be obtained by any other method.

All these cases healed without the slightest difficulty and without discomfort to the patient.

Mr. H. V. Forster said he would like to add a note to Mr. C. P. Wilson's introductory remarks on methods of operative approach to the post-nasal space. The surgical removal of nasopharyngeal fibroma was a formidable task and the associated bleeding especially alarming. He had, as assistant, seen Mr. Thomas Guthrie successfully remove these growths and deliver the tough material more easily through the nose by performing a submucous resection of the bony outer wall of the pyriform aperture.

Mr. S. W. G. Hargrove said that he had 2 cases of fibroma of the post-nasal space in small boys, aged 11 and 8. They both had very large fibromas which were growing forwards into the nasal cavity. In both cases he split the soft palate longitudinally in the mid-line. He removed the major part of the tumour from behind, but being unable to remove it completely owing to the forward growth into the nasal cavity, he then performed a right-sided Norman Patterson's approach to the ethmoidal region. In both cases he was able, by using the post-nasal approach and the anterior approach through the ethmoid, to remove the tumour completely. When approaching the tumour from the post-nasal space he found, in both cases, that the tumour was so large he was unable to remove it by the post-nasal approach.

He would like to ask whether Mr. Wilson would be able to remove the tumours in these cases by his post-nasal approach. In trying to remove the tumour from the post-nasal space approach he found that he was working at an angle to the cribriform plate, and by using the approach through the ethmoidal region he found that he was able to work parallel to the cribriform plate. Thus by using these two approaches he was able to remove the tumour completely.

There was no scarring on the face. The position he adopted at operation was the same as Mr. Wilson's, with a Boyle-Davis gag in position and the patient in a half-sitting position, at an angle of 45 degrees. He did the first part of the operation splitting the palate and using the Boyle-Davis gag to keep the mouth open, and then approaching the tumour through the right ethmoidal region. There was no post-operative difficulty in healing of the palate.

He also had a case of choanal atresia on the right side, which he had dealt with by the same method and had obtained a good result. Having seen Mr. Wilson's approach to the post-nasal space, he would have preferred to use Mr. Wilson's method instead of splitting the palate longitudinally. But if the tumour extended into the nasal cavity then a combination of an anterior and posterior approach would be necessary.

Mr. J. D. Gray thought Mr. Wilson would be interested to know of an independent discovery of this approach. Mr. Wilfred Hynes, the Plastic Surgeon in Sheffield, discovered it two years ago when experimenting in extensive mobilization for cleft palate repair. Recognizing it as a good approach to the nasopharynx he passed on the information to the Otologists.

Mr. C. P. Wilson, in reply, said he did not know why this operation was not done many years ago. It was just an idea that occurred to him and not the result of research but having found it was useful he felt other people should also have the chance of trying it.

Mr. Hogg operated with the patient lying on the right side and as he was right-handed Mr. Wilson thought he would have much greater difficulty in suturing the palate than if the patient were lying on his back as he would then have his elbow free.

He used three or five stitches and not three or four as one was in the mid-line. He could see no value in the use of a dental mirror after the nasopharynx had been opened.

He agreed with Mr. Hargrove that if a nasopharyngeal tumour passed forward into the nose it might not be possible to remove it from behind and a decision must be made in any particular case as to how the anterior portion could best be dealt with.

Replying to Mr. Simpson he agreed that the transverse part of the incision was essential. If it was intended to explore the anterior part of the nasopharynx on one side the incision could be enlarged downwards on that side only, but if it was decided to inspect particularly the posterior part or fossa of Rosenmüller then the incision should be enlarged downwards on the opposite side.

Mr. J. C. Hogg, also in reply, said that the question of a mirror seemed to have aroused criticism but he knew of no other method by which one could look into the back of a nose. He used it to see whether he had made a large enough hole for the patient to breathe through afterwards.

Section of Dermatology

President—W. N. GOLDSMITH, M.D., F.R.C.P.

[*November* 16, 1950]

Necrobiosis Lipoidica Diabeticorum Resembling Deep Type Granuloma Annulare (Two Cases).—R. E. CHURCH, M.B. (for C. H. WHITTLE, M.D., F.R.C.P.).

Case I.—H. A., aged 47. Agricultural worker.

Five months ago the patient noticed sudden onset of blurring of vision in the right eye. This was diagnosed as thrombosis of the central retinal vein and the patient was found to have diabetes mellitus. (Blood sugar at that time 0·302%.) The diabetes is now controlled with soluble insulin and diet.

Skin lesions have been present on the arms and the backs of hands for about one year and on the left shin for six months.

Family history.—Father, mother and one sister diabetic.

On examination.—Numerous circinate plaques on both aspects of the forearms varying from 1 to 2 cm. in diameter and on the dorsa of both hands in larger confluent plaques. The lesions are dusky red in colour, some flat and others with a raised yellowish edge resembling granuloma annulare.

On the outer aspect of the left shin is a flat shiny yellowish plaque, 2 cm. in diameter with a telangiectatic centre and a dusky red border typical of necrobiosis lipoidica.

Biopsies from a deep nodule on the hand and from the shin lesion:—

Histological report (Dr. A. M. Barrett): In both specimens there are relatively large areas of necrosis in the corium at all levels down to the subcutaneous fat. The collagen fibres are still preserved in the necrotic areas but their staining reactions are altered and the nuclei of the cells have either disappeared or have disintegrated into fine chromatin fragments. Around the necrotic areas there are zones of cellular infiltration in which histiocytes predominate; often they are arranged in palisade fashion.

In the specimen from the leg at least one small blood vessel has its lumen almost occluded by cellular intimal thickening.

In the specimen from the arm there is one small necrotic focus in the subpapillary zone which has a fibrinoid centre and in its general appearance resembles granuloma annulare; but I think it may well be merely a variant of the other lesions.

Mucicarmine and thionin preparations fail to demonstrate mucin. Scharlach R preparations show that the necrotic foci contain fine droplets of fat in small amount.

I think that the histological findings in both lesions are consistent with a diagnosis of necrobiosis lipoidica diabeticorum.

Case II.—S. F., aged 62. Smallholder.

Eleven years ago onset of diabetes mellitus, which has been treated with diet and soluble insulin; the patient becomes easily unstabilized and has had repeated hypoglycæmic comas.

Nine years ago nodules appeared on each wrist and subsequently on the left forearm.

On examination.—Left forearm, ulnar aspect: a brownish red plaque 4 × 3 cm. with hard yellowish nodules on the border forming an annular lesion.

Left wrist: an irregular red base 5 × 2·5 cm. dotted with pea-sized yellowish nodules.

Right wrist: two nodules 0·3 cm. diameter yellow in the centre on a red base.

Many of the lesions are not attached to the epidermis and the skin is movable over them.

Investigations.—Blood cholesterol 193 mg.% (normal range 100–230 mg.%).

Histology (Dr. A. M. Barrett): A strip of skin with a rounded nodule of degenerate fibrous tissue situated rather deep in the corium. A narrow zone of cellular reaction is present round the border of the nodule. There is considerable thickening of the walls of small arteries in the corium adjacent to the nodule and some have well-defined foci of lymphocytes near or around them. Mucicarmine and thionin preparations fail to demonstrate mucin. Frozen section stained by Scharlach R shows numerous fine droplets of fat within the nodule. The histological picture resembles that of necrobiosis lipoidica diabeticorum.

Comment.—Since attention was drawn to the histological resemblances between necrobiosis lipoidica diabeticorum and granuloma annulare (Bernstein, 1937), various means of differentiation have been described. In necrobiosis lipoidica the zones of necrobiotic collagen are usually less well defined than in granuloma annulare, and although the so-called palisading of the cellular infiltrate around the necrobiotic collagen may be found in both lesions it is less marked in necrobiosis lipoidica and the cellular infiltration is more diffuse. Fibrosis of the walls of blood vessels and proliferation of their intimal lining is usual in necrobiosis lipoidica and uncommon in granuloma annulare, although it may occur in the deep type (Jacobi, 1931).

Lipoid deposits in the necrobiotic areas are a feature of necrobiosis lipoidica and are not found in granuloma annulare. In one case published as granuloma annulare containing lipoids (Ellis and Kirby-Smith, 1942) the patient was a diabetic and the lesions are described as nodules and plaques of a yellow colour occurring on the forearms, back, buttocks and legs, the diagnosis before biopsy being xanthoma. This may, in fact, have been a similar case to Cases I and II described above.

The presence of mucin is an almost constant finding in granuloma annulare; Prunty and Montgomery (1942) and Freudenthal (1945) found that it thus differed from necrobiosis lipoidica, in which mucin is absent.

As to the site of the lesions, while we have become accustomed to associating necrobiosis lipoidica with the shins, Oppenheim's original case (1929) had lesions on the upper and lower extremities, trunk, buttocks, palms, soles and face and in fact 20% of published cases have had lesions on other areas, the wrists being the second site of election.

These two diabetics show in one case a typical plaque of necrobiosis lipoidica on the shin with nodular lesions on the arms and in the other case very similar nodular lesions on the arms alone. Clinically they resemble the deep type of granuloma annulare, but the general histology is more in favour of necrobiosis lipoidica, mucin is absent and lipoids are present in all the lesions; we therefore conclude that they are a clinical variation of the usual lesion of necrobiosis lipoidica.

REFERENCES

BERNSTEIN, J. C. (1937) *Arch. Derm. Syph.*, **36**, 282.
ELLIS, F. A., and KIRBY-SMITH, H. (1942) *Arch. Derm. Syph.*, **45**, 40.
FREUDENTHAL, W. (1945) *Brit. J. Derm.*, **57**, 177.
JACOBI, F., in JADASSOHN, J. (1931) Handbuch der Haut- und GeschlKr., **10**, 798. Berlin.
OPPENHEIM, M. (1929) *Zbl. Haut- u. GeschlKr.*, **32**, 179.
PRUNTY, F. C., and MONTGOMERY, H. (1942) *Arch. Derm. Syph.*, **46**, 394.

Granulomatosis Disciformis Chronica et Progressiva (Miescher).—G. C. WELLS, M.B., and W. N. GOLDSMITH, M.D.

P. A., aged 48. Master Mariner.

History.—A small red patch was first noticed on the left shin about ten years ago, which has gradually extended. He knocks his shins from time to time climbing up the companion way.

There is a small atrophic erythematous lesion in front of the left ear, but this was treated in India two years ago with radon seeds and later with carbon dioxide snow, and was probably a rodent ulcer.

His general health has been satisfactory and there has been no serious illness. For several years he has had mild dyspepsia, for which he was recently investigated at the Hospital for Tropical Diseases under the care of Sir Neil Hamilton Fairley, to whom we are indebted for much of the clinical data.

On examination.—On the left shin there is a sharply defined oval lesion, 4 × 6 cm., with an elevated border about 2 mm. wide. The centre is sclerosed and atrophic, it has a brownish colour, and dilated venules can be seen through a waxy, slightly scaling surface.

On general physical examination there is no evidence of disease, except for eunuchoidism secondary to imperfect descent of the testes.

Investigations of blood and C.N.S. normal. Mantoux 1 : 1,000 positive. Skiagram of chest: No abnormality apart from some pleural thickening at the left base. Radiological examination of the gastro-intestinal tract and gall-bladder : No abnormality except for two diverticula in the transverse colon.

A biopsy was made through the edge of the lesion of the left shin on October 13, 1950:—Histopathology: The epidermis is thinned and there is scarring in much of the dermis. In the dermis and in the hypodermis there are numerous areas of intense granulomatous reaction arranged round small vessels which show degenerative changes in their walls. The cellular reaction varies from one focus to another, consisting of epithelioid cells, lymphocytes, plasma cells and many giant cells, both of Langhans and of foreign-body type. No organisms are seen in sections stained with Ziehl-Neelsen's or with Gram's stain. Examination with polarized light shows no doubly refractile particles.

Comment.—The clinical appearance of the lesion is suggestive of necrobiosis lipoidica, except for its well-defined narrow raised edge. The histological picture is striking and is that of a tuberculoid granuloma. There is, however, nothing elsewhere to support a diagnosis of chronic infective granuloma due to tuberculosis, leprosy or syphilis.

Miescher and Leder (1948) described under the title of "Granulomatosis disciformis chronica et progressiva (atypische Tuberculose)" two cases with distinctive clinical and histological features. Mali (1950) described two further cases under the same title.

In these cases there were lesions on the legs which were very slowly progressive and which resembled necrobiosis lipoidica diabeticorum clinically, except that they showed some granulomatous nodules and rather sharply defined borders. Histological sections showed an intense granulomatous reaction round the walls of blood vessels of the skin and subcutis. While these authors were uncertain as to the exact nature of this condition, they considered that the lesions were probably tuberculous.

It is probable that the same condition has previously been described under various titles. For instance Gougerot and Fernet (1923) described "Sarcoides en nappe sclérodermiformes des membres inférieurs", and Goldsmith (1929) described "a case of clinical morphœa with tuberculous histology", these cases having much in common with those described by Miescher.

ADDENDUM.—Sections subsequently stained with thionin showed no mucin.
The serum cholesterol was 335 mg. per 100 ml.

REFERENCES

GOLDSMITH, W. N. (1929) *Brit. J. Derm.*, **41**, 226.
GOUGEROT, H., and FERNET, P. (1923) *Bull. Soc. Franç. Derm. Syph.*, **30**, 245.
MALI, J. W. H. (1950) *Dermatologica*, **101**, 84.
MIESCHER, G., and LEDER, M. (1948) *Dermatologica*, **97**, 25.

The President: Whether there is a relation between this condition and necrobiosis lipoidica really hinges upon the question as to whether in the latter the necrobiotic change is primary or secondary. I incline to the view that the necrobiosis is the *result* of the granulomatous process.

Xanthomatosis of Skin.—H. J. WALLACE, M.R.C.P.

R. M., male aged 14.

This patient was shown here on December 1948 with a clinical and histological diagnosis of lichen nitidus (*Proc. R. Soc. Med.*, **42**, 343).

The lesions have since increased in size and number and an orange colour has appeared in the centre of some of them.

No evidence of disease elsewhere.

Histology (Dr. I. Whimster): A xanthoma—the majority of the lipoid present stains poorly or not at all with Scharlach R but is doubly refractile.

Blood cholesterol 160 mg.%.

Urine two hours after ingestion of 50 grammes glucose showed no evidence of sugar.

Idiopathic Acanthosis Nigricans.—PETER M. INMAN, M.D.

Miss T. L., aged 56.

She was first seen at the end of June 1949 with a few weeks' history of warts and skin irritation, especially of the axillary regions and the head. There had been genital irritation and pruritus ani some months previously. There were numerous wart-like lesions of axillæ, groins and both temples. The skin of axillæ, groins, anus and bends of elbows was thickened and rugose, having a mammillated appearance and covered by a marked blackish pigmentation, some of which would rub off on to a piece of white lint. A diagnosis of acanthosis nigricans was made and she was admitted to the Sunderland Royal Infirmary, where the following investigations were performed:

Fasting test meal: Slight increase of hydrochloric acid. Barium meal and follow through normal. Barium enema: Diverticulitis of iliac, transverse and ascending colon. Occult blood: One positive test followed by two negative tests.

Urine: Pus cells and *B. coli* infection. Intravenous pyelogram normal. Blood urea 26 mg./100 ml.

X-ray of chest: No abnormality.

Blood count: Hb 96%; White cells 4,900; Film—no abnormality.

The pelvic organs were examined by Mr. D. A. Sanford under anæsthesia. No abnormality was found apart from acute retroflexion of the uterus. She had been noted to be markedly hypertensive. Her own doctor stated that she had suffered from phlebitis before the onset of the skin disorder. Since no cause for the acanthosis nigricans had been discovered, she was referred by her own doctor to another dermatologist who advised laparotomy. This was accordingly performed by Mr. D. A. Sanford, who found no abnormality beyond a simple retention cyst of the right kidney. Sections of this, as well as of the left axillary skin, were taken at the time of the operation in October 1949.

Histology (Dr. J. Tregillus): Section of left axilla: There is irregular acanthosis and hyperkeratosis with lengthening of the interpapillary processes. Pigmentation of the basal layer is unusually prominent. There is some increase of small round cells in the superficial layers of the corium.

From December 5, 1949, she was treated by 300,000 units of vitamin A daily for six weeks without improvement. Treatment with 5 grain yeast tablets, nine daily, was then substituted, also without improvement.

In January 1950 in view of recurrence of frequency of micturition and a history of transient hæmaturia the previous year, a cystoscopy was performed with negative results.

Comment.—For the last five and a half years, until the onset of the disease, the patient has been nursing her mother, who weighs 12½ st., and has had to lift her in and out of bed. I wondered whether this lifting had resulted in some sympathetic damage. (In a case reported by Pawlof[1], juvenile acanthosis nigricans developed following a blow on the abdomen and this might conceivably have operated through damage to the sympathetic fibres in the upper abdomen.) I should like any comments on treatment, and to learn whether it is the opinion of members that she is likely to develop carcinoma.

Dr. Brian Russell: I saw this patient after all investigations had proved negative and still felt justified in recommending an exploratory laparotomy owing to the common occurrence of carcinoma in these cases.

Is it possible that the acanthosis nigricans and any carcinoma that may coincide are both due to a common unknown cause of skin and mucosal stimulation to hyperplasia with a resultant marked tendency to carcinoma at various mucosal sites, rather than the acanthosis being secondary to any such carcinoma?

Dr. R. M. B. MacKenna: In answer to the point raised about the association of acanthosis nigricans with malignant disease it might be worth while to quote the belief of several observers that in acanthosis nigricans associated with carcinoma the acanthosis does not develop until metastasis has occurred, even though the metastasis may be so small as not to be found at an ordinary laparotomy.

The following cases were also shown:

Poikiloderma Atrophicans Vasculare.—Dr. J. R. SIMPSON.

Pemphigus Erythematodes.—Dr. PETER BORRIE.

Sclerædema Adultorum of Buschke.—Dr. H. T. CALVERT and Dr. G. A. BECK.

Ischæmic Ulcers of Leg.—Dr. R. H. MEARA and Dr. W. N. GOLDSMITH.

Unusual Case of Lichen Planus.—Dr. J. MORGAN.

Lymphatic Leukæmia of the Skin.—Dr. OLIVER SCOTT.

(These cases may be published later in the *British Journal of Dermatology*.)

[1] Pawlof (1902) *Monatshefte*, **34**, 269 (with references); quoted by Ormsby, O. S. and Montgomery, H. in "Diseases of the Skin", London, 7th Ed., 1948, p. 581.

Section of Odontology

President—Sir WILLIAM KELSEY FRY, C.B.E., M.C., M.D.S.Durh., F.D.S., M.R.C.S.

[*January* 22, 1951]

The Problem of "The Clicking Jaw"

By V. E. IRELAND, M.B., B.S., L.D.S.

Plastic and Jaw Injuries Unit, East Grinstead, Sussex

IT is not many years since the treatment of lesions of the temporo-mandibular joint was regarded as the exclusive province of general and orthopædic surgeons. A growing appreciation in recent years of the importance of dental factors in the ætiology of many of these conditions is at last resulting in the direction of these cases to the dental surgeon.

In many of the American publications on this subject the emphasis has been on the auditory symptoms which are believed to result from lesions of the temporo-mandibular joint. In my experience cases in which there are auditory symptoms are rare. The only cases encountered so far have been undoubted examples of otosclerosis. The purpose of this paper is to consider more closely the symptoms which definitely accompany disorders of the temporo-mandibular joint, in an endeavour to show the mechanism of their production and indicate a rational approach to their prevention and treatment.

SYMPTOMATOLOGY AND CLINICAL FINDINGS

In a series of consecutive cases the patients may be grouped according to their presenting symptoms, as follows:

(1) Painless clicking during the opening phase.

(2) Intermittent "locking" during which the opening is temporarily limited to about one fingerbreadth and usually accompanied by pain.

(3) Limitation of opening with pain with a history of previous symptoms.

(4) Limitation of opening with pain without previous symptoms.

(5) Clicking, or more accurately jolting, at maximum opening and again at the beginning of the closing phase.

(6) A combination of (1) or (2) with (5).

A typical patient in the first group is in the late teens or early twenties, with a history that the clicking began suddenly and spontaneously, or that it came on after some injury. The noise is quite often loud and may be audible to others as well as to the patient. It usually occurs when the mouth is about half-way open, but it may occur anywhere from quite early to almost the end of the opening movement. The patient is aware of a feeling of obstruction during the movement of opening, the click occurring as the obstruction is overcome. The rest of the opening movement and the whole of the closing movement are free of symptoms. Careful palpation or auscultation over the joint reveals that in addition to the loud noise during opening there is a faint click during the final 2 or 3 mm. of the closing movement.

In the majority of cases there is a deep over-bite resembling that of Angle's Class II Division 2. Very often some or all of the molars have been lost. In some cases with apparently well-formed dental arches, the first molars have been lost early to obviate crowding, and this

appears to be responsible for the deep over-bite. Sometimes there is a single dental factor such as a misplaced tooth, in an otherwise normal dental arch, which prevents the teeth coming together into their normal occlusal relationship. In nearly all except these last instances the free-way space is larger than normal. The term free-way space denotes the difference between the intermaxillary distance in the incisor region when the mandible is in the rest position and when the teeth are in occlusion.

Radiographically, the condylar head appears to be posterior to its normal position and there is a backward movement of the condyle as the mandible moves from the rest position into the position of occlusion (Figs. 1 and 2).

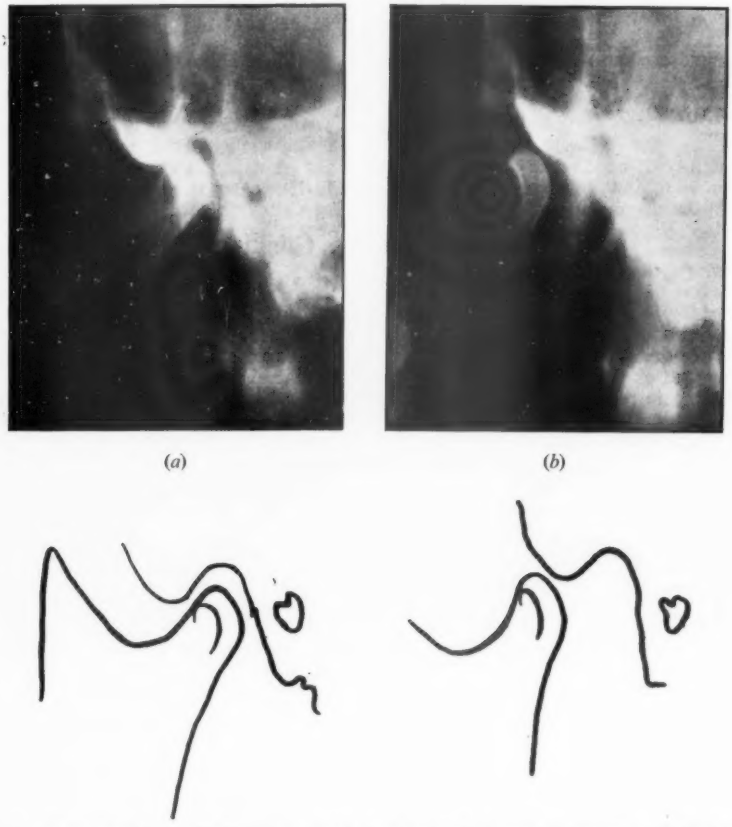


FIG. 1.—Tomographic sagittal sections (with tracings) of a normal temporo-mandibular joint showing the relationship of the condylar head to the articular eminence in (*a*) the closed, (*b*) the open positions.

A striking clinical feature of this type of case is that if the teeth are prevented from coming into occlusion by placing something between them, as by a thin rod held across the upper arch in the canine region, the clicking is eliminated.

Cases of this kind are not always free from pain. When the clicking has been present for a long time, and especially in women of neurotic type, pain over the area of the joint may be a feature. Occasionally some pain is present from the onset of clicking or it may even precede it.

A patient of the second group presenting himself for the first time complains that the jaw becomes locked, usually on waking, and for a time the mouth can only be opened a few millimetres. He has severe pain over the affected joint which is made worse by attempts to open the mouth wider. By making some manœuvre of the jaw, often by pressure over the

joint, the patient is able to "unlock" the jaw and restore normal movement. The pain and tenderness persist for a time. In nearly all cases there is a history of clicking of the affected joint and when examined while the jaw is free the clinical findings are identical with those of the first group. The change in symptoms sometimes appears to have been spontaneous but more often there is a history of some trauma though this may have been slight. A slight blow on the chin; attempting to take a very large bite of a hard apple, "the free gratification of an inclination to yawn or sneeze", as Pringle (1918) puts it, may have brought about the change. Quite often there is a history of a recent dental extraction. This need not necessarily have been a difficult extraction of a lower molar, though that may well be the precipitating factor. On the contrary, when only one or two molars are in occlusion the loss of an upper molar may have a profound effect on jaw function, and precipitate symptoms.

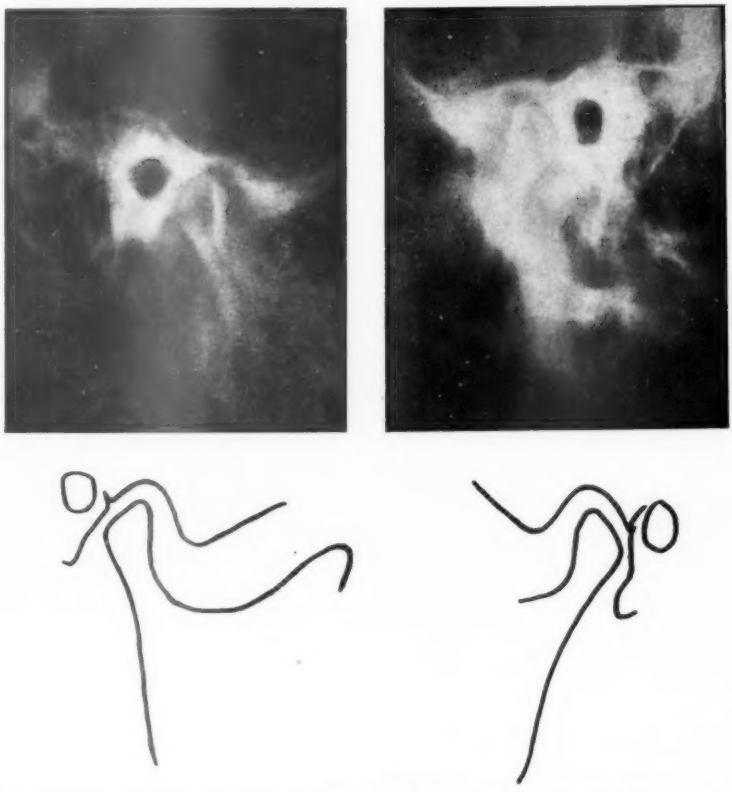


FIG. 2.—Note the backward displacement of both condyles in a typical case of painless clicking. Both sides are shown in the closed position.

A patient of the third group seen within a few days of the onset of symptoms complains of continuous aching pain centred over the affected joint radiating down to the angle of the jaw, and often also to the side of the head and to the ear, and occasionally to the mastoid region. The opening of the mouth is limited to about one fingerbreadth which makes eating difficult as well as painful. Usually there is a history of painless clicking for some months or years with recent episodes of temporary "locking" which have become more frequent, and increasingly difficult to "unlock". On the last occasion the usual manœuvre, by which the patient was previously able to "unlock" the jaw, failed. Examination reveals tenderness over the joint and often hyperæsthesia over the temporal and parotid regions. The limited opening, which no longer causes any clicking, is accompanied by deviation of the mandible to the affected side. Lateral movement of the mandible to the opposite side is limited and

increases the pain, while lateral movement towards the affected joint is usually full and without pain. Clearly there is an obstruction to the forward gliding movement of the condyle on the affected side. Careful observation of the teeth as they come into occlusion may reveal that this is accompanied by a lateral movement.

X-rays (Fig. 3) show that the condyle, posteriorly displaced when the teeth are in occlusion, as in Group 1 cases, does not move forward when the mouth is opened. It sometimes descends vertically for a short distance, the joint space remaining appreciably wider than normal.

It is evident from the foregoing that the symptoms of the first three groups correspond to the first, second and third stages of the same underlying process. Together they constitute what will be called Type I cases. It should be pointed out that although Type I cases usually go through all three stages they occasionally start at the second or even at the third. In this latter event it will be very difficult to distinguish the case from one belonging to the next group—Group 4.

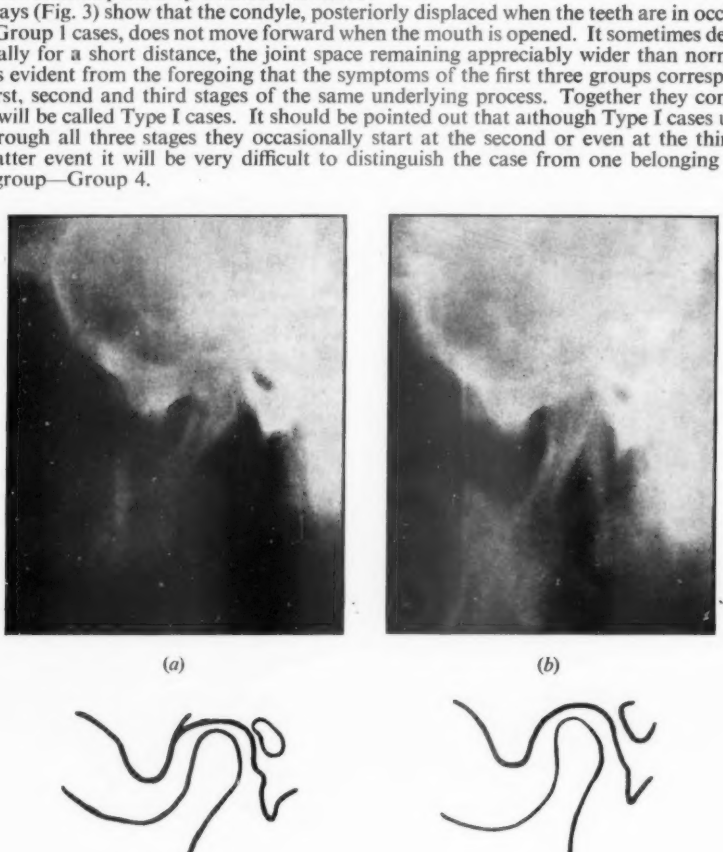


FIG. 3.—This patient had painful limitation of movement. Tomograms show absence of forward gliding of the condyle; (*a*) shows the closed and (*b*) the open position.

Symptomatically, Group 4 cases are very similar to those of Group 3 but they are usually distinguishable by the absence of a history of clicking and by the absence of abnormalities of either teeth or jaws. Except for the limited forward gliding of the condyle on the affected side and some widening of the joint space there is no radiographic abnormality.

The pain (which is severe) is sudden in onset, usually while eating or it may follow a severe blow on the jaw. There may be slight swelling over the affected joint. Another distinctive feature of the Group 4 cases is the tendency to settle down spontaneously after a few weeks, leaving no abnormality.

Patients of the fifth group experience what must be described as a jolt of the mandible, sometimes accompanied by a noise which is more of a hollow knock than a click, just as maximal opening is reached and again as the closing movement commences. It is usually bilateral and the "jolts" on the two sides are not quite synchronous, but follow one another in rapid succession so that the mandible is seen to perform a small jerk to one side and then back to the mid-line. The simple test which eliminates clicking in the Type I case is without effect. Pain is not usually a feature of these cases and many patients are unaware that their jaw movement is abnormal. Radiographically, they are indistinguishable from the normal in which the condylar head rides well on to the antero-inferior surface of the articular eminence when the mouth is fully open.

The fourth and fifth groups are thus clinically distinct from each other and from the Type I cases and will be called Types II and III respectively.

The sixth group has been included because cases in which the symptoms of either the first or second group are combined with those of the fifth are not uncommon. However, they possess most of the clinical features of the Type I case and run a similar course. The original six groups may thus be arranged as follows (*see* table):

1. Painless clicking during opening phase ..	1st stage	Type I
2. Intermittent "locking"	2nd stage	
3. Limitation of opening with pain with history of previous symptoms.. ..	3rd stage	
4. Limitation of opening with pain without history of previous symptoms.. ..		Type II
5. Click or jolt occurring at maximum opening and again as closing phase begins		Type III
6. Combination of 5 with 1 or 2		Types III and I

The Mechanism of Clicking

Before considering the mechanism by which the symptoms are produced it will be helpful to note certain structural features of the joint. In its simplest terms the temporo-mandibular articulation is a hinge joint in a movable socket; the fibro-cartilaginous disc is attached very firmly to the condyle at its poles so that normally it follows the condyle in all its movements and allows only a simple hinge movement to occur in the lower compartment of the joint.

The upper surface of the disc articulates with the postero-inferior surface of the articular eminence. It is only the thin central part of the disc which is concerned in withstanding such pressure as is transmitted to the joint during biting and chewing. Behind and above this thin central part the disc is thickened and softer, forming a cap on the condyle. Behind this thickening the disc thins rapidly and is blended with the capsule. Below and anterior to the thin central part there is another less well-marked thickening of the disc to which part of the lateral pterygoid muscle is inserted through the capsule. The capsule allows considerable free forward gliding movement in the upper joint compartment during which the condyle rides not only on to the summit of the eminence but often some distance on to its antero-inferior aspect. Some rotation of the condyle about its vertical axis and some lateral movement, the Bennett movement, is also possible.

The normal movement in opening the mouth is brought about by a combination of hinge movement in the lower compartment and forward gliding in the upper. It has been shown by Thompson (1946) that the movement of the mandible from the position of occlusion to the rest position is a pure hinge movement. Beyond this point gliding movement is increasingly evident, becoming predominant as maximal opening is approached. During closure this order is reversed and again the mandible passes from the rest position to the occlusal position by a pure hinge movement.

It is important to view the articulation of the mandible with the base of the skull as a single entity. Not only are there the two mandibular joints coupled together, but the two complexes also articulate through the teeth attached to them. When the mouth is open the mandibular joints and muscles and ligaments attached to the mandible, as well as the force of gravity, determine the position and path of movement of the mandible. When the teeth are in contact, they, as it were, dictate the position of the mandible.

Because of the mutual effect of the articulation of the teeth and the mandibular joints during development a high degree of harmony normally results, so that when the mandible moves from the rest position to the occlusal position the teeth meet exactly in their correct relationship. It will readily be seen that conflict between the "needs" of the joints and the "dictates" of the dental articulation may arise. Thus pain caused by biting on the gum flap over an erupting wisdom tooth may compel the patient to adopt a "bite of comfort" in which the teeth are brought together with the mandible deviated to one side. An over-erupted upper wisdom tooth, when the lower is missing, may impinge on the distal aspect of the

lower second molar and cause a forced lateral deviation of the mandible to the opposite side each time the teeth are brought into occlusion.

Loss of posterior teeth may allow the bite to close and cause the mandible as a whole to be forced in a backward direction by the action of the inclined planes of the incisors. Since the rest position of the mandible is virtually constant this closing of the bite results in an increase in the free-way space, and the movement of the mandible from the rest position to the occlusal position is no longer a pure hinge movement. The condyles are driven into a position above and behind their normal position in relation to the articular eminence. Only one condyle is affected when a unilateral cause is responsible, but when the bite has closed, both are affected.

This forced displacement of the condyle occurs each time the teeth are brought together in biting and chewing. If growth and development of the condyle and teeth have not ceased compensatory changes may occur to restore harmony. The fact that only a small proportion of people who have lost posterior teeth develop joint symptoms, suggests that such compensatory changes frequently occur. If only a single tooth or perhaps two teeth are responsible for the forced movement, the conflict may be resolved by the loosening of these teeth and the appearance of localized paradental disease. When the teeth do not give way and compensatory changes cannot occur, the condyle is forced into the abnormal position hundreds of times a day and the structures of the joint are subjected to a constantly recurring strain. In patients who grind their teeth during sleep, there is no respite for the joint.

The joint itself must be regarded as an important link in the proprioceptive mechanism co-ordinating the action of the muscles of mastication. Any disturbance of the joint is therefore likely to interfere with muscular co-ordination and cause abnormal forces to be transmitted to the joint. This will tend to perpetuate and even increase the joint disturbance. The use of only anterior teeth also imposes an added load on the joint.

As in other joints prolonged excessive stress and altered mechanics of the joint ultimately cause degenerative changes. In the temporo-mandibular joint this leads to loosening of the attachments of the disc to the condyle. Only a slight injury, which would be quite without effect on the normal joint, is then needed to start the train of symptoms described in the Type I case.

With the attachment of the disc to condyle thus loosened the disc is no longer compelled to follow the condyle when it moves into its abnormal position, so that during the final few millimetres of the closing movement the thickened upper part of the disc rotates forward to lie between the condyle and the postero-inferior surface of the eminence. This movement of the disc causes the faint click heard during this movement. In some people it is actually possible to feel what is certainly the edge of the disc being thrust laterally and forwards when this occurs.

When the mouth is opened the normal relationship of the condyle and disc is not immediately restored but the disc and condyle move together, both pulled by the lateral pterygoid, for a variable distance on to the postero-inferior surface of the articular eminence when pressure on the thick part of the disc and tension on its posterior attachment to the capsule causes the disc to slip back with a snap into its correct position on the condyle. Thereafter during the rest of the opening phase and all but the last two or three millimetres of the closing phase, the condyle and disc maintain their correct relationship. If this final two or three millimetres of the closing movement is prevented, the relationship of the condyle and disc is not disturbed and both opening and closing movements are free from clicking. This is, of course, what happens in the simple clinical test mentioned earlier, and in treatment the aim is to provide some permanent means of preventing the abnormal final part of the closing movement.

Once the disc has been sufficiently loosened from the condyle for clicking to occur the possibility of further damage to the joint is greatly increased. Not only is the posterior part of the disc subjected to pressure which it is ill-fitted to withstand, but the disc and condyle undergo additional trauma each time the click is produced. These factors alone may be enough to cause a low-grade traumatic arthritis in the joint. Further loosening of the disc increases the difficulty of restoring the correct relationship of the disc to the condyle, after displacement, which inevitably leads to the symptoms of intermittent locking, the thick upper part of disc remaining temporarily in front of the condyle acting as an obstruction to its forward movement.

It is a short step to the third stage where the locking has become permanent. The disc is then no longer a gliding socket for the condyle and even the hinge movement occurs in an abnormal socket ill-fitted for such a purpose. This represents a severe disturbance of the mechanism of the joint; not only will it give rise to pain in and around the joint, and to reflex pain particularly in the area of distribution of the auriculo-temporal nerve which supplies the joint, but limitation of movement of the one joint will impose a severe additional burden on the other, which ultimately may also give rise to symptoms. The low-grade

inflammatory process due to the constant trauma to the soft tissues of the disorganized joint may also ultimately give rise to bony changes in the condyle. Clinically, the picture will then be one of osteoarthritis.

What happens in Type II where painful limitation of opening starts suddenly while eating, without previous symptoms, can only be guessed; perhaps as a result of some unguarded unco-ordinated movement the disc gets severely nipped in some way, or more likely, as Professor Rushton has suggested to me, a villus of the synovial lining gets nipped in the joint. If there has been a severe blow on the jaw the explanation is simple. Clinically, the result in any case is an acute traumatic arthritis with an effusion into the joint cavity or cavities. It has already been noted that in this type and in the painful stage of Type I, the mandible may make a lateral movement as the teeth come into occlusion. This must not be confused with the lateral movement caused by a misplaced tooth. The effusion and œdema of the soft tissues within the joint have caused some separation of the joint surfaces and shifted the axis of rotation of the mandible. In other words the lateral movement is a manifestation of the lesion in the joint, not as in the other instance, its cause. It is clearly important to recognize this distinction and avoid the error of grinding the teeth to make them harmonize with the temporarily deranged joint. With rest the condition tends to settle down and return to normal.

In Type III the condition may be regarded as a subluxation of the joint. The condyle moves well beyond the summit of the articular eminence, but instead of doing so smoothly, as in many normal cases where the condyle reaches this point, it does so with a jerk. A similar jerk occurs when the condyle passes the summit of the eminence during closure. During the opening movement the elevator action of the muscles seems to be insufficiently inhibited, and the pull of the lateral pterygoid too strong; while in the closing movement the elevator parts act strongly before the retracting parts of the muscles have brought the condyle behind the summit of the eminence. Clearly a very high degree of co-ordination of muscle action is necessary to accomplish this part of the movement smoothly. A relatively slight injury, such as may be caused by dislocation during a dental extraction under general anæsthesia, may well upset the delicate neuromuscular mechanism and start this jerky movement.

It must here be mentioned in passing that some people can produce an impressively loud snap or click in their temporo-mandibular joints voluntarily. The mechanism by which this is done is very similar to that in the type under consideration, except that the muscular inco-ordination is deliberate. The mouth is opened wide so that the condyle is a little in front of the eminence. The elevator parts of the muscles are then made to act strongly a little before their retracting effect is brought into play. In this way the condylar head is made to spring back as soon as it reaches the summit of the eminence.

Reverting to the involuntary condition, here again the abnormal movement is itself injurious to the structures of the joint and tends to perpetuate the trouble and even make it progressively worse. This is particularly likely to occur when there is a large over-jet between the incisor teeth and the mandible must be protruded to its maximal extent when biting on the front teeth. In this position the condyle is no longer firmly supported on or behind the summit of the eminence and the joint structures are subjected to abnormal stress.

The condition may become a true luxation, or by weakening the attachment of disc to condyle may predispose to clicking of the first type described. Fortunately, the patient usually exercises sufficient care and avoids opening the mouth to its maximum extent and the progress of the condition is interrupted with, in some cases, a spontaneous return to normal.

Treatment

In Type I, should there be a normal free-way space treatment consists in a search for, and elimination of, causes of a "bite of comfort" or a misplaced tooth causing a forced deviation of the mandible as the teeth come into occlusion. This is usually not very difficult but in some cases it is worth while to adopt the procedure described by Lindblom (1948) which he calls "bite analysis". It should be pointed out, however, that success with this procedure is entirely dependent on the accurate registration of the rest position of the mandible.

In Type I cases with a large free-way space, treatment consists in making a bite splint or bite plane which prevents the mandible from closing more than 2 mm. beyond the rest position. In this way the forced backward movement of the mandible and condyles is prevented and in the majority of cases painless clicking is eliminated. It cannot be too strongly emphasized that this is not the same as bite-opening, the object is rather to fill in the abnormal free-way space and restore the mandible to its correct working position.

If the lower molars are missing a partial lower denture with extensions over the occlusal surfaces of the premolars can be used. If all the teeth are present the bite splint can be made

to cover the occlusal surfaces of the upper molars and premolars. Such an appliance is better tolerated in the upper jaw and it interferes less with speech. At the bite stage in the construction of the splint or denture measurements are made between marks on the face, or better still, on the incisor teeth when the mandible is in the rest position. The bite rims are built up and trimmed to give fairly uniform contact and to prevent closure beyond the rest position. Then with only the surface of the wax softened the patient closes, biting very lightly a further 2 mm. into the wax. The patient must be sitting comfortably and relaxed with the head unsupported. The bite rim must be replaced after cooling, and the closing movement repeated several times to make sure that each time the teeth pass exactly into the same position as they come into contact with the wax without any lateral deviation. If the clicking is not eliminated the procedure should be repeated allowing only ½ to 1 mm. closure beyond the rest position. If, as sometimes happens, this still fails, or only partly succeeds in preventing clicking, one must on no account be tempted to build up the bite beyond the rest position as this may have disastrous results. The bite splint is processed in clear acrylic. A lingual or palatal bar is used to keep the appliance as small as possible. The occlusal surface of the splint is trimmed so that only a very shallow impression of the cusps of the opposing teeth remain. Such a bite splint should be worn all the time and on no account left out at night. If after being worn for several months the appliance has proved successful, the question of some more permanent prosthesis must be considered. Whether this takes the form of a removable denture or over-lay denture, or fixed bridges, it is as well to remove all misplaced tilted teeth from the opposing jaw, so that there is a reasonable chance of restoring a good articulation by making the prosthesis to replace these and other missing teeth, at the same time as the permanent replacement of the bite splint is made. This work is best carried out using an anatomical articulator with face-bow registration and using the temporary bite splint when mounting the study models in the centric position.

So far the treatment of only those cases with painless clicking and intermittent locking has been considered. It is among these that dental treatment has the best prospect of success. This is particularly encouraging when it is realized that this is the early stage of a process which if left unchecked may lead to a serious condition for which, in many cases, only surgical treatment offers relief and that not without risk. Whenever possible, therefore, the case should be tackled at this stage. It would be better still to spot what might be called the potential "clickers" before the symptoms start. Ideally, much could be done by well-planned orthodontic and prosthetic treatment to prevent a given individual from becoming even a potential case.

If a patient is seen shortly after the onset of painful limitation of movement, the third stage of Type I, it is worth while to attempt a manœuvre such as that described by Pringle (1918) to reduce the displacement of the disc. A general anæsthetic may be needed for this. If this is successful the mandible should be immobilized in the rest position for about two weeks and then treated as a first or second stage case.

It should be mentioned here that at the onset of this condition the patient may experience the severest pain. It is one of the few instances among these conditions where a course of shortwave diathermy to the joint and muscles affords relief.

If the manœuvre just mentioned is not successful in restoring normal movement or the condition has been present for some time, the first step is to construct a bite-splint in precisely the same way as that already described, but with a smooth occlusal surface. This will not only prevent the forced movement of overclosure, but will eliminate all lateral stress and allow the mandible to take up its new position as œdema within the joint settles down. In a proportion of cases this brings relief, and the patient becomes free from all except occasional pain and regains sufficient mobility in the joint to eat without undue difficulty. When this has been achieved the construction of a permanent appliance, on the lines already described, can be undertaken.

If after a reasonable trial of these measures, either the pain or the limitation of movement or both are unrelieved, surgical treatment must be contemplated.

The evaluation of the various forms of surgical treatment is beyond the scope of this paper; at the Maxillo-Facial Unit at East Grinstead, in cases of long standing, especially with severe limitation of movement or bony changes in the condyle, condylectomy has been found to give better results than extirpation of the disc. It is important to regain good movement in the false joint following condylectomy by using a training flange attached to a lower cast cap splint.

Extirpation of the disc probably has a place in the treatment of the early case, shortly after the onset of pain and limitation; but the tendency for symptoms to return with crepitation in the joint after some months or years cannot be ignored. In any case every effort must be made to establish a sound functional dental articulation after operation; not only to make the best of the new joint but to try to save the other joint from a similar fate.

For the Type II case—the acute traumatic arthritis—immobilization in the rest position, and a course of shortwave diathermy to the joint, ensure speedy relief from pain and a more certain and rapid restoration of normal function than if the mandible is left free. Alternatively, if the patient is not willing to have his jaw immobilized, a bite splint with a smooth occlusal surface may be used. The splint is worn only until the pain has gone.

In the third and last type of case—if the subluxation is of a mild degree no treatment, beyond an injunction to the patient that he must avoid opening his mouth to the full extent, may be necessary. If there is a marked over-jet of the incisor teeth it would be rational to correct this.

For the more severe case, there is a rather unattractive choice between several forms of surgical treatment and the use of a sclerosing agent injected in the joint. They all have as their objective the limitation of the forward gliding movement of the condyle, and they are all more or less successful in achieving this, whether it is by an osteoplastic operation to produce a bony stop on the summit of the eminence, or by dividing the attachment of the lateral pterygoid or by making a fascial sling around the joint. But when it is recalled that a simple arthrotomy also produces limitation of movement of the joint, it is clearly difficult to assess the merits of a particular operation.

The use of a sclerosing agent injected into the joint as described by Schultze (1937) has the merit of simplicity and freedom from the risk of injury to the facial nerve involved in any operative procedure on the joint. It cannot, however, be warmly recommended as it undoubtedly achieves its effect by causing an acute arthritis which results in adhesions within the joint as well as the peri-articular fibrosis claimed for it by the originators of this treatment.

In this paper the relatively common lesions of the temporo-mandibular joint have been considered. Only a brief reference has been made to the neurotic element which is often an important feature. Edentulous cases have not been dealt with separately, as they do not differ essentially from those discussed. The relatively rare cases of gradual limitation of movement in elderly patients with senile osteo-arthritic changes, and in younger patients with polyarthritis involving the temporo-mandibular joint, have not been considered.

I should like to express my indebtedness to the Nuffield Foundation which enabled me to visit the Scandinavian countries for studies on this subject. I am also deeply grateful to Sir William Kelsey Fry and Mr. Terence G. Ward for their help and encouragement in the preparation of this paper.

REFERENCES

LINDBLOM, G. (1948) *Dent. Rec.*, **68**, 254.
PRINGLE, H. (1918) *Brit. J. Surg.*, **6**, 385.
SCHULTZE, L. W. (1937) *J. Amer. med. Ass.*, **109**, 1032.
THOMPSON, J. R. (1946) *J. Amer. dent. Ass.*, **33**, 151.

Mr. R. S. Taylor: I have operated on a number of cases of clicking jaw that have not yielded to treatment on the lines described by Mr. Ireland. Of the 20 cases operated on since November 1948, 5 have been so recent that it is not possible to assess the results. Of the remaining 15 patients, 12 have shown definite improvement, and 3, little or no improvement. The operation performed was reinforcement of the capsule with a fascial strip, the object being to limit the excessive forward movement of the condyle. About one-third of the patients operated on were men.

It would be interesting to know what difference Mr. Ireland found as regards the incidence in the two sexes.

I do not think that trauma is by any means the only cause of clicking jaw, the condition is frequently seen in young people of poor muscle tone, and in middle-aged females of a neurotic type.

Mr. R. J. G. Grewcock: In his Address Mr. Ireland has dealt almost exclusively with temporo-mandibular derangement due to the *retruded* position of the condyle, omitting any mention of a protracted position with the teeth in occlusion.

I have in mind a patient giving evidence of much pain and crepitation in a joint in which X-rays showed the condyle to be eroded and antero-posed on the eminentia. Its fellow condyle was retroposed, and the joint without symptoms. Can Mr. Ireland tell us whether he has experience of similar derangement occurring as the result of advanced position of the condyle?

The relation between malocclusion and temporo-mandibular joint disorders has been closely investigated in Sweden and two main courses adopted for treatment. The *radical* method as exemplified by Karl Boman, who in his works published in 1947 describes the results obtained by extirpation of the disc in over a hundred cases. His conclusions lead him to state categorically that "clicking" in the joint is due to an overriding of the edge of the meniscus by the condyle, either anteriorly or posteriorly due to lack of concurrent traction of the disc during movement. Crepitation and clicking always cease following extirpation. Secondly, that repeated trauma as the result of malocclusion can often initiate temporo-mandibular joint disorders.

The *conservative* school, as supported by Lindblom, Beyron and others, prefers, quite naturally, to rely on bite analysis and any requisite bite adjustment, with restoration to the normal of the occlusal vertical dimension, before the rather serious operation of extirpation is even contemplated. From the many excellent results seen, I would make a plea for more intensive co-operation between

surgeon and dental surgeon in this country, to ensure that bite adjustment is tried before extirpation of the disc is attempted.

REFERENCES

BEYRON, H. (1945) Procedure of selective grinding, *Svenska Tandl-Sällsk. Kurs., Stockholm.*
BOMAN, K. (1947) *Acta chir. scand.* (suppl. 118) **95**, 1.
LINDBLOM, G. (1936) *Dent. Cosmos*, **78**, 1227.

Mr. Hamish Thomson: Why do some patients presenting with a temporo-mandibular joint disturbance show signs of a displaced bite while others with a similar bite displacement have no upset in the joint? Why do some joints which "click" during movement produce no pain while others do? What, broadly speaking, constitutes a "click" in the joint and what causes the pain? What, in other words, is the pathological process? Yet why in some joints which have "clicked" for years does there seem to be no such process? Some light may have been cast on these problems by Professor R. J. Last, who maintains that there is no pressure exerted by the condyle in the fossa during normal closure. Further, he states that not only is there no cartilage in the meniscus of the temporo-mandibular joint, but that it is a relatively vascularized tissue. It may be, then, that there is a possibility of tissue recovery following the trauma that may produce the disturbances under discussion.

With regard to treatment, there is no doubt that, in the majority of cases, by freeing the bite with a simple acrylic splint, and so resting the joint, symptoms and signs of joint disturbance disappear. The chief problem in the treatment of these cases is how to maintain the bite at the new height. A warning as to the effect of prosthetic treatment of the bite, in relation to the joint, may be worth while, and may point to the limitation of this line of treatment. The muscles which maintain the jaws and provide their functional force tend to restore the bite to its original position at the expense of the investing tissues of the teeth. Care should be taken that too optimistic an alteration in the bite height is not made and that due regard be paid to the rest position of the mandible. This may point, in turn, to the part played by the musculature in disturbances of the joint. J. R. Thompson (Chicago) has suggested to me that a neuromuscular imbalance may be a factor in these disturbances.

Mr. C. F. Ballard: I would like to correct one impression that Mr. Ireland has given. A normal incisor contact is not a sliding one, and therefore whatever happens to the vertical dimension in the buccal segments a sliding contact is not going to produce distal displacement of the mandible. Mutilation of the buccal segments may, of course, be followed—and frequently is—by a change in the incisor occlusion. However, abnormal incisor relationship due to abnormal axial inclination of the teeth, or due to abnormal dental base relationship (the first may follow early loss of deciduous teeth), may result in a sliding contact which, through sensory stimulation, might produce a posterior displacement of the mandible. The sliding contacts associated with excessive overbite of typical Angle's Class II, Division 2, abnormalities, and some Angle's Class II, Division 1, abnormalities, have again no relationship to the vertical dimension of the dento-alveolar structures in the buccal segments. They are the result of abnormal axial inclination of the teeth associated perhaps, but not always, with abnormal dental base relationship. There is a possible explanation of the mechanism of posterior displacement in the fact that we know that the posterior horizontal fibres of the temporal muscle are used for retraction of the mandible. It might be argued that in these sliding contacts either in incisor and canine region, or in premolar region, sensory, including proprioceptive, stimulus causes a reflex contraction of the posterior fibres and some of the vertical fibres of the temporal muscle just when, in fact, the muscles should be reflexly relaxing as the teeth come into occlusion. This contraction would not only produce a posterior displacement but would also account for the excessive free-way space which is so frequently seen in these cases. It disturbs the normal balance between the main muscles of mastication at the time of occlusion and the vertical development of the dento-alveolar structures in favour of the former, so balancing the development of the latter at what is a true overclosed position. It is important to remember that in the normal, vertical development of the dento-alveolar structures is in physiological balance with muscle action. Any disturbance of occlusion might reflexly disturb muscle action, alter this delicate balance and produce joint symptoms.

Mr. Ireland, in reply, stated that about two-thirds of his cases were women.

He had encountered two cases resembling the one mentioned by Mr. Grewcock. In these, the position of the condyle was normal but the clinical features suggested that the disc or part of the disc was behind the condyle. The mandible deviated to the opposite side on opening, and lateral movement towards the affected side increased the pain.

He stressed the fact that observations of the mechanism of clicking during operations on the joint, or by contrast arthrography, were often misleading. Apart from the difficulty of such observations because of the inaccessibility of the joint the operative interference itself, whether under local or general anæsthesia, completely altered working conditions of the joint.

In reply to Mr. Hamish Thomson he agreed that there is probably no pressure exerted on the condyle in the normal joint, at least when biting on the posterior teeth, and considered this an added reason why pathological changes occur when the joint is subjected to pressure associated with the various dental factors discussed.

The fact that many of the early cases of clicking do respond to the simple measures advocated lent support to the view that the tissues of the joint are capable of recovery.

In reply to Mr. Ballard he considered that it is the further closing of the bite following loss of buccal teeth in cases of Angle's Class II, Division 2, which is responsible for posterior displacement of the mandible, the inclined planes of the incisor acting either directly or possibly by a reflex mechanism as suggested by Mr. Ballard.

Adaptation of the Mandibular Condyle Following Fracture

By ALEXANDER MACGREGOR, M.A., M.D., F.D.S. R.C.S.

A MALE epileptic in a mental institution, during the course of a fit, fell and sustained a fracture of the condyle and coronoid process of the mandible on the right side. X-rays taken at the time (Figs. 1*a*, *b*) revealed these fractures and treatment consisted merely of bandaging and rest. Five months later the patient died of an intercurrent disease, and at a post-mortem the mandible was obtained. The mandible (Fig. 2*a*) shows the site of the fractures, but also shows that the condyle in spite of the gross alteration in position appears reunited with the ramus with firm bony union. The coronoid process, though not so displaced as the condyle, has also united with the ramus. It will be seen from the photographs (Fig. 2)

FIG. 1*a*.

FIG. 1*b*.

FIGS. 1*a* and *b*.—Lateral oblique and postero-anterior views of the mandible taken a few days after the injury, showing fracture of the right condyle and coronoid.

FIG. 2*a*.

FIG. 2*b*.

FIGS. 2*a* and *b*.—Views of mandible to show union of right condyle with ramus in spite of gross angulation, rounding off of lateral side of neck of condyle to form new articulating surface, and elongation of right coronoid.

that the condylar head has become somewhat moulded on its upper aspect in an apparent attempt to reform an articulating surface. The coronoid process has also become modified in shape, presumably due to the alteration in direction and strength of the muscular forces. The sound condyle on the left side shows some alteration in the shape and superficial appearance of the bone, presumably also due to the slight changes in muscular pull necessitated by the alteration in the opening and closing mechanism.

Comment.—With a fracture of the condylar neck of any severity, the usual tendency is for the condyle and neck to assume a more horizontal position with the condylar head directed inwards. It has been thought by many that bony union did not occur under such circumstances and that the remains of the condylar neck on the ramus became rounded off, thus forming a false joint. X-rays of numerous cases of fractures of the mandibular condyle, taken both before treatment and some time afterwards at the Plastic & Jaw Centre of Hill End Hospital, have not borne out this contention. It is difficult to be positive from X-ray appearances, particularly since the distance moved by the condylar head in opening and closing of the mouth is not great. In all cases, however, which have been X-rayed some months after the fracture, whether treatment was by fixation or not, movement of the displaced condylar head appears to take place with the ramus in an open and closed position. The case described shows that bony union can occur between the fractured and displaced condylar head and the ramus of the mandible in a comparatively short time, even though no real fixation has been applied. The case is also of interest in showing the moulding of the condylar head and the coronoid process on the right side which has followed their alteration in position, and the consequent compensatory alteration in the shape of the sound left condylar head.

I would like to record my gratitude to Dr. H. I. Coombs, who made the specimen available to me, and also to Miss N. Walker, who took the photographs.

BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

Åkerblom (B. V.). Standing and sitting posture: with special reference to the construction of chairs. pp. 187. Stockholm: Nordiska. Kr. 12.50. 1948.

Benson (J. R., 2nd Baron Charnwood). An essay on binocular vision. pp. 117. London: Hatton Press. 1950.

Holmstrom (J. E.). Bibliography of interlingual scientific and technical dictionaries. pp. 220. Paris: U.N.E.S.C.O. 4s. 0d. 1951.

Jackson (J. H.). Selected writings. 2 vols. London: Hodder & Stoughton. 1931–32.

Jones (E.). Essays in applied psycho-analysis. New edit. Vol. 1. Miscellaneous essays. pp. 333. London: Hogarth. 21s. 0d. 1951.

Josiah Macy, Jr. Foundation. 20th anniversary review of the Josiah Macy, Jr. Foundation, 1950. pp. 110. New York: (Foundation). 1950.

King (E. S. J.), Lowe (T. E.), and Cox (L. B.), ed. Studies in pathology presented to Peter MacCallum. pp. 350. Melbourne: University Press. 35s. 0d. 1950.

Kostelijk (P. J.). Theories of hearing. pp. 180. Leiden: Univ. pers Leiden. 12s. 0d. 1950.

Leonardo (R. A.). Yearly surgical digest. pp. 293. New York: Froben Press. 1950.

Mahfouz (Naguib Pacha). Atlas of Mahfouz's obstetric and gynæcological museum. 3 vols. Altrincham: Sherratt. £9 9s. 0d. 1949.

Masani (K. M.). Ectopic pregnancy. pp. 165. Bombay: Popular Book Depot. 1949.

Santos (C.). A radiologia perante o problema dos corpos estranhos. 2 vols. Lisbon. 1944.

Sterling-Winthrop Research Institute. (Illustrated account.) pp. 63. New York. 1950.

Strachan (G. I.). Textbook of obstetrics. pp. 731. London: Lewis. 1947.

Van Pelt (S. J.). Hypnotism and the power within. pp. 201. New York: Skeffington. 18s. 0d. 1950.

Ward (R.). The design and equipment of hospitals. pp. 360. London: Baillière, Tindall & Cox. 42s. 0d. 1949.

Williams (L.). Minor medical mysteries. pp. 211. London, Toronto, etc.: Cassell. 5s. 0d. 1935.

Section of Anæsthetics

President—W. ALEXANDER LOW, M.C., M.B., B.S., F.F.A. R.C.S.

[*January* 5, 1951]

An Assessment of Flaxedil (Gallamine Triethiodide, B.P.)

By A. G. DOUGHTY, M.B., B.S., D.A.
Anæsthetist, Kingston Group of Hospitals
and
W. D. WYLIE, M.B., M.R.C.P., D.A.
Anæsthetist, St. Thomas's Hospital

Dr. W. D. Wylie: Flaxedil, or Gallamine triethiodide, as it is now named by the British Pharmacopœial Commission, is a British production of a synthetic curarizing agent (called tri-(β-diethylaminoethoxy)-benzene triethiodide) which was first synthesized in France by Bovet, Depierre and de Lestrange (1947). The first report on Flaxedil from this country was by Mushin, Wien, Mason and Langston (1949). They showed that Flaxedil produced muscle paralysis by neuromuscular block, that it exhibited a sparing effect on respiration, that it was effectively counteracted by neostigmine and that its period of action was shorter than that of tubocurarine.

Flaxedil has several possible clinical advantages when compared with tubocurarine and it is convenient to discuss some of the evidence substantiating this view. There is also a somewhat problematical disadvantage, namely tachycardia, which is worthy of further comment.

EXPERIMENTAL FINDINGS

Rapid breakdown.—Fig. 1 illustrates that Flaxedil is eliminated from the body more quickly than tubocurarine. This experiment was carried out on cats. The procedure was to inject

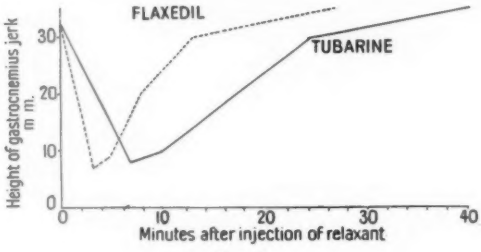


FIG. 1.

sufficient relaxant to produce a known depression of the normal gastrocnemius jerk of the cat. This ensured equipotent dosage and illustrated that the return to normal occurred about ten minutes sooner after Flaxedil than after tubocurarine.

Respiratory sparing effect.—Mushin *et al.* showed that in a comparison of the effect of these two relaxants on the gastrocnemius jerk in cats, a dose of Flaxedil which caused 100% depression left respiratory ventilation at 30% of normal, whereas with tubocurarine

respiratory ventilation was 25% of normal. They also showed that when decamethonium iodide was used the respiration was 45% of normal. On the conscious volunteer Mushin *et al.* showed that doses of about 40–70 mg. of Flaxedil could be tolerated without demonstrable decrease in pulmonary ventilation. The actual dosage given to any individual was estimated as that necessary to produce complete paralysis of the flexor muscles of the forearm as assessed by a dynamometer and of the muscles of the abdominal wall. Our experiments on conscious volunteers are in general agreement with this, though we have found that the paralysis is complete within one to one and a half minutes as against four minutes, and that even when neostigmine is given diplopia may persist for about one to two hours in some cases. Moreover, using a dose of ½ mg. per kilogram of body-weight, there is some diminution of maximum inspiration recorded on a spirometer, though not so great as with an equivalent dose of tubocurarine.

An assessment of the relative effect of the relaxants on respiration has been made on clinical cases under normal conditions of anæsthesia. This has appeared important and a recent paper by Paton and Zaimis (1950) has stressed the disadvantage of conscious volunteers who may have an abnormally high circulatory adrenaline, a fact which militates against a drug like decamethonium iodide. Clinically two series of cases serve to illustrate the respiratory sparing effect of Flaxedil. In a series of 70 upper abdominal operations anæsthesia was induced with a small dose of thiopentone and maintained at a light level with cyclopropane. A muscle relaxant was injected just before the surgeon incised the skin. The dose injected was either 20 mg. of tubocurarine or 100 to 110 mg. of Flaxedil, these being the rough equivalents suggested by Mushin *et al.* 45% of the cases given tubocurarine needed artificial respiration for some period of time as against 10% of the Flaxedil cases. The second series was of cases in which a muscle relaxant was used to facilitate intubation. Anæsthesia was with thiopentone, nitrous oxide and oxygen. Table I shows our results on 243 cases.

TABLE I

	Percentage of easy intubations				Percentage of easy intubations (Groups I and II) requiring artificial respiration
	Group I Very easy	Group II Easy	Group III Difficult	Group IV Failed	
Flaxedil 80 mg. 136 cases	27·9	52·2	16·2	3·7	8
		80·1			
Tubocurarine chloride 20 mg. 50 cases	26	50	18	6	26·3
		76			
Decamethonium iodide 4 mg. 57 cases	22·8	42·1	24·6	10·5	59
		64·9			

It was found before this series was started that the equivalent dosages of the three relaxants needed to produce an easy intubation were 80 mg. of Flaxedil, 20 mg. of tubocurarine and 4 mg. of decamethonium iodide. With these dosages it can be seen that the percentage of easy intubations is about equivalent for all relaxants. But the effect on respiration is considerably less with Flaxedil than with either of the others. Although we have included our experiences with decamethonium iodide we do not suggest that this is evidence of a marked respiratory depressant effect with this drug. The mode of action of decamethonium iodide at the neuromuscular junction is different from that of tubocurarine or Flaxedil, and its clinical effect on individual muscle groups varies also. The results show the limited effect of Flaxedil on respiration, and confirm its value as an aid to intubation. Incidentally they suggest that decamethonium iodide is not so satisfactory for facilitating intubation unless used in larger doses and then with consequent respiratory depression.

Counteraction by neostigmine.—The most interesting experimental results have been those which illustrate the very effective and immediate counteraction of the paralysis induced with Flaxedil by neostigmine. Fig. 2*a* shows a tracing of the depressant action of Flaxedil on the gastrocnemius jerk of the rabbit. The immediate, complete and sustained antidote effect of a dose of neostigmine is well illustrated. The procedure was to inject sufficient relaxant to produce depression of the gastrocnemius jerk to somewhere between 10 and 50 per cent of its initial height. A large dose of neostigmine was then injected and the return of the jerk to normal recorded. A large dose of neostigmine was used to ensure that its action was maximal. As will be seen when tubocurarine is injected (Fig. 2*b*) the effect of neostigmine, even when a considerably larger dose is used, is complete and sustained, but only completed over a period of ten minutes. Fig. 3 shows the direct comparison of these results on a graph.

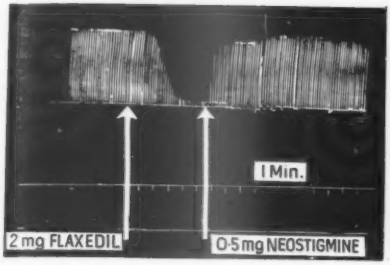


FIG. 2*a*.

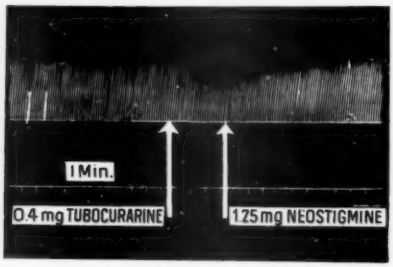


FIG. 2*b*.

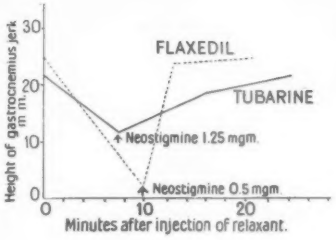


FIG. 3.

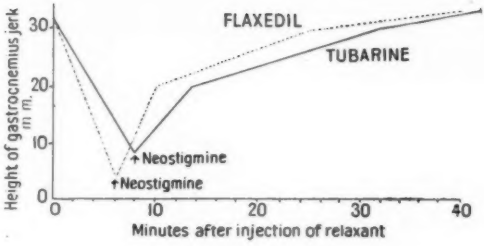


FIG. 4.

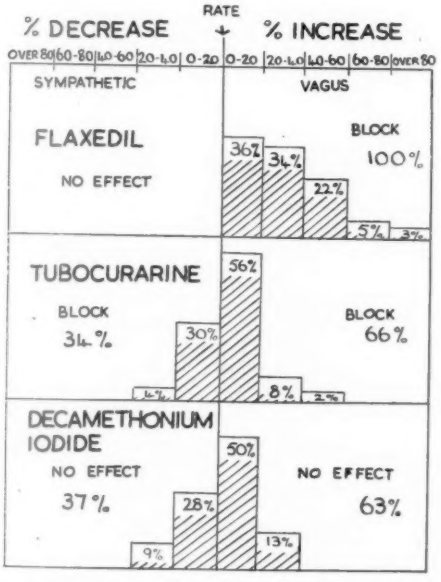


FIG. 5.—Pulse changes related to effect of relaxant on autonomic system.

Fig. 4 shows the results of a similar series of experiments carried out on the cat. Here the results are not so dramatic but nevertheless in keeping, and serve to illustrate the clinical impression that Flaxedil is completely and rapidly counteracted by a small dose of neostigmine—a point which is worth considering when it is appreciated that, apart from the remote possibility of neostigmine affecting the heart, there may be other systemic effects such as salivation and colicky abdominal pain, despite the buffering effect of atropine, when a dose of over 2·5 mg. is used. This point was confirmed on the conscious volunteer.

Tachycardia.—Occurrence: It is our opinion that tachycardia occurs frequently when Flaxedil is used. Indeed we believe that under certain conditions it is universal. Fig. 5 illustrates the results of 243 cases intubated under thiopentone anæsthesia coupled with a relaxant. Anæsthesia was maintained by nitrous oxide-oxygen sequence. For the conditions of the experiment the normal pulse-rate was taken as that found at rest in the ward before the operation. The dosages of Flaxedil, tubocurarine and decamethonium iodide were 80 mg., 20 mg. and 4 mg. respectively. The dosage of thiopentone was assessed as twice the sleep dose in every case and the pulse was taken at regular intervals over the ensuing period of the operation. The percentage increase over normal was recorded as the average of these readings. It will be seen that an increase in pulse-rate occurred in every case after the use of Flaxedil. There was a 20% increase in 56% of cases after the use of tubocurarine and a 20% increase in 50% of cases after decamethonium iodide. The significant factors are the absence of a decrease in pulse-rate in any case in which Flaxedil was used and the increases in pulse-rate of from 20% to 40% and 40% to 60% after Flaxedil as compared with the two other relaxants. It might be considered that the conditions of this experiment were too variable to offer a true comparison, but comparable results were obtained by stabilizing anæsthesia with thiopentone and nitrous oxide-oxygen sequence over a few minutes, estimating the pulse-rate and then injecting the dose of relaxant intravenously.

General considerations: Several interesting points emerge. The onset of tachycardia is practically immediate and coincident with the expected onset of curarizing effect. It occurs within one to one and a half minutes after the injection of Flaxedil and remains for a longer period of time than is apparent from the curarization of the patient. Moreover it appears to occur in some degree whatever the dose of Flaxedil. If 20 mg. of Flaxedil are injected during the course of a simple operation under light anæsthesia, though no apparent curarizing effect appears yet there is invariably an increase in pulse-rate. Moreover, additional injections of Flaxedil during the course of a long operation tend to reproduce a tachycardia or to sustain a pre-existing one, though there is little to suggest a summation effect in this respect.

The tachycardia is simple and uncomplicated. Continuous and frequent electrocardiographic recordings have shown no irregularity of rhythm. Indeed the absence of irregularities under light anæsthesia despite surgical stimulus has been a striking factor—always provided that the relaxation induced has been adequate. This factor, though, is common to the use of all relaxants in adequate doses.

Relationship of tachycardia to other factors: The direct cause of the tachycardia is the injection of Flaxedil into the body, but though the onset is almost immediate, its occurrence at all is dependent to some extent on one other factor, and that is the general anæsthetic agent. If cyclopropane is used for anæsthesia then the tachycardia may or may not occur, depending on the level at which anæsthesia is maintained. But with all other anæsthetics it varies very little. The type of premedication and the type of surgical stimulus, apart from direct operative procedures on the heart and its vicinity, exert very little influence. Though the level of adrenaline in the conscious patient may exert a considerable effect, nevertheless in the majority of such people there is a definite increase in pulse-rate associated with the injection of Flaxedil. This was assessed not only on volunteers, but on patients to whom a test dose was given prior to anæsthesia. The effect of a dose of neostigmine, even though buffered with atropine, was to produce an immediate decrease in pulse-rate. Furthermore it has been possible to produce some degree of tachycardia in patients with such differing pre-existing pulse-rates as a bradycardia of 50 beats a minute and a tachycardia of 120 beats a minute.

Causation of tachycardia: In an attempt to find the causation, animal experiments were carried out on both cats and rabbits, but it proved impossible to produce tachycardia either reflexly or by direct action on the heart in either of these animals. Table II gives a typical series of results when Flaxedil was injected into the left femoral vein of a cat. Recordings of the heart beat were taken on a moderately fast-running kymograph to distinguish individual beats, and connected via a mercury manometer to a cannula in the carotid artery. The direct action of Flaxedil on the heart was assessed by a perfusion experiment on the isolated heart.

TABLE II

Experiment	Dose of Flaxedil mg./kilo	Heart-rate Beats per 15 secs. Before injection Flaxedil	15/20 secs. after injection	At height of depression of jerk	% depression of gastrocnemius
1	0·4 mg.	48	50	—	—
2	0·4 mg.	50	52	48	30
3	0·65 mg.	55	56	49	90
4	0·8 mg.	58	56	57	95

(Normal heart-rate for cats is 50 per 15 secs. approximately.)

The control of the heart-rate is the balanced result of vagal and sympathetic action on that organ, either of which may be indirectly or directly affected by anæsthesia. A glance at Fig. 5, which further illustrates our results on intubated cases under nitrous oxide and oxygen anæsthesia, would suggest that Flaxedil is the only one of these three relaxants to have an unbalanced action. In fact we know that decamethonium iodide has little effect on either sympathetic or vagal ganglia and that tubocurarine affects both. Flaxedil blocks vagal ganglia only, and has little effect on the sympathetic. It is interesting to note the relative effect of tubocurarine and Flaxedil on the autonomic ganglia. Table III is taken from

TABLE III

	Ratio of curarizing action to autonomic block action Sympathetic	Vagus
Flaxedil	40	4–6
Tubarine	4	1–2·5

(After Jacob and Depierre, 1950.)

a recent paper by Jacob and Depierre (1950) and shows the ratio of the curarizing activity to the autonomic block activity. These figures imply that 40 times as much Flaxedil is needed to block the sympathetic completely as is needed to produce muscle paralysis, whereas only 4 to 6 times as much is needed in the case of the vagus. With tubocurarine 4 times the curarizing dose is needed to block the sympathetic as against 1 to 2·5 times for the vagus. The ratio of sympathetic blocking dose to vagal blocking dose of Flaxedil would therefore be 8 : 1 as compared with 2 : 1 for tubocurarine. Without doubt the effect of Flaxedil on the vagus predominates over its effect on the sympathetic, while with tubocurarine by comparison the effect is not so unbalanced. Nitrous oxide exerts no effect on the vital organs of itself, but cyclopropane exerts a direct effect on the sino-auricular node and conducting mechanism of the heart. Thus it circumvents vagal block, and of its own accord may depress the cardiac rate. This accounts for the fact that tachycardia is not universally found when Flaxedil is used with cyclopropane anæsthesia. Ether has little or no effect on the increased heart-rate induced by Flaxedil. It is interesting, too, to compare the effects of an injection of a known vagal inhibitor such as atropine on the human. If a dose of 1/50 gr. (1·3 mg.) is given intravenously there is an immediate increase in pulse-rate of from 10 to 40 beats per minute. The failure to produce tachycardia in cats and rabbits may be explained by their considerable lack of vagal tone as compared with the human. Any alteration in that tone might therefore be expected to produce a less marked effect in these animals than in the human. However, Wien (1950) has recently produced tachycardia in dogs when using Flaxedil, and when their vagal tone has been increased by morphine.

From these results we would suggest that tachycardia occurring clinically when Flaxedil is used is due to vagal block unaccompanied by sympathetic block.

Implications of tachycardia: A rapid action of the heart affects that organ in two ways. First it causes the ventricles to expend more energy and second it shortens the time for recovery between beats. The actual heart-rate and the duration of the increased rate are factors to be noted when assessing the clinical implications of a tachycardia, but most important are the reserves of the heart. If the heart is relatively normal then it is extremely unlikely that a tachycardia such as that produced by Flaxedil could produce any serious disturbance. However, if the reserves are already diminished then a tachycardia might conceivably exhaust them and lead to the possibility of acute cardiac failure. Clinically we have had no cases in which a tachycardia produced by Flaxedil could be said to have caused trouble in this way, but we feel that in prolonged major surgery on patients with pre-existing cardiac disease Flaxedil may not be the relaxant of choice.

Other vagal block effects.—A knowledge of the effect of Flaxedil on the autonomic system has led us to look for other associated phenomena. We have already shown the advantage

of Flaxedil for intubation, and how a dose of 80 mg. is equivalent for this purpose to 20 mg. of tubocurarine. This may be due to the specific effect on the vagi which depresses the glottic and associated reflexes. This effect also would be expected to dilate rather than constrict the bronchial tree, and though there is no clinical or experimental proof to show that this is the case, experience with Flaxedil during bronchography has suggested that it occurs.

An interesting effect of the unilateral action is frequently seen when hypertensive patients are anæsthetized and when Flaxedil is used for relaxation. It is a peculiarity of patients with arteriosclerotic disease that they react more actively to drugs which affect the sympathetic ganglia than otherwise normal individuals. This is noticeable for example when pentamethonium bromide is used for controlled hypotension, since only a small dose is needed in such cases. Similarly with Flaxedil it is not uncommon to see a rise of blood pressure and usually a maintenance of the normal. Wilson and Gordon (1949) in their paper on Flaxedil noted the rise in blood pressure and attributed it to light anæsthesia. However when tubocurarine is used on similar patients one expects some slight fall.

Histamine release.—Both Flaxedil and tubocurarine liberate histamine, but the amount is considerably less with Flaxedil. In animal experiments Mushin *et al.* showed that with Flaxedil the amount of histamine was 1/5 to ½ less than with tubocurarine, and an injection of Flaxedil into the arterial supply of the hindleg of a dog had no effect. When tubocurarine was injected there was a slight fall of pressure and dilatation of the vessels. Dos Santos and Soares (1950) have injected tubocurarine intra-arterially in the human and produced swelling and œdema of the limb, whereas with an equivalent dose of Flaxedil there has been no effect. We have noted no effects which we could reasonably put down to histamine other than some flushing of the skin and possibly a slightly increased bleeding at the site of operation. However the use of antihistaminics has not diminished these effects. Interestingly enough on some conscious volunteers there was a marked flushing of the skin and a great sense of warmth associated with the onset of paralysis. We have had no cases of bronchospasm nor gross hypotension associated with the use of Flaxedil.

Fate of Flaxedil in the body.—Flaxedil is not broken down in the body. It is excreted unchanged by the kidneys and thus an adequate renal function is a prerequisite for its use. It has been estimated that the greater proportion of a given dose is eliminated within two hours and to this extent any further doses given within this period are bound to be cumulative. From our experience we do not believe that people show a sensitivity to Flaxedil nor that a previous dose renders that person sensitive to a further dose. We feel that a second dose given before complete elimination of the original dose, even though no apparent curarization persists, may lead to an enhanced effect simply due to cumulation. As with tubocurarine, the addition of a central respiratory depressant or of a small quantity of ether may produce an effect which is easily mistaken for excessive neuromuscular paralysis by the relaxant.

Dr. A. G. Doughty:

Clinical Findings

From the point of view of the clinical anæsthetist there are four important differences between Flaxedil and tubocurarine. These are:

I. With Flaxedil there is a greater margin between muscular relaxation and diaphragmatic paralysis.

II. Flaxedil has an equally effective but shorter period of action.

III. Flaxedil's action is more readily and rapidly reversed by neostigmine.

IV. Flaxedil does not lower the blood pressure.

We will now describe the use of Flaxedil in clinical anæsthesia under these four headings and will attempt to show how the experimental findings may be applied in practice.

I

Abdominal relaxation.—The most important role of the relaxants in anæsthesia is undoubtedly the production of relaxation of the abdominal wall without resort to deep general anæsthesia. Anæsthetists are now very familiar with the scope of action of tubocurarine in anæsthesia for abdominal surgery, so by this yardstick the properties of Flaxedil may conveniently be judged.

Mushin has estimated that a dose of 15 mg. of tubocurarine is approximately equivalent in curarizing potency to 80 mg. of Flaxedil. Clinical use of the two drugs for abdominal surgery has confirmed the accuracy of this estimate.

There is a very wide variation in the techniques used in administration of relaxants for this purpose, so it is difficult to compare and contrast tubocurarine and Flaxedil with any degree of accuracy. We propose to mention two commonly used techniques, because we believe that they best serve to illustrate the differences between the drugs under discussion. These are, firstly—induction with thiopentone, injection of relaxant, and maintenance of anæsthesia with cyclopropane without controlling the respiration; and secondly—induction with thiopentone, injection of a paralysing dose of relaxant, followed by controlled respiration with nitrous oxide and oxygen, relaxation being maintained by subsequent small increments of relaxant as required.

With the first technique, namely thiopentone, single dose of relaxant and cyclopropane without controlled respiration, there seems to be little difference in the quality of the relaxation provided by the two drugs, or in the time for which relaxation lasts. It is possible, of course, that the anæsthetist instinctively compensates for the shorter period of action of Flaxedil by maintaining the patient at a slightly deeper level of anæsthesia. The difference between the two drugs is apparent on comparing the character of respiration. With Flaxedil, the characteristics of third-plane chloroform anæsthesia are simulated. Breathing is quiet, the respiration mainly diaphragmatic, but there is still sufficient tone left in the lower intercostals to fix the lower ribs so that the diaphragm can contract in a co-ordinated manner. With tubocurarine in equivalent doses, paralysis of the lower intercostals is more marked, and a pronounced chin-tug is an indication of the inco-ordination and the relative inadequacy of the diaphragmatic respiration. This advantage of Flaxedil over tubocurarine is particularly welcome in gynæcological laparotomies when respiration may be embarrassed by the Trendelenburg position and abdominal packs.

With the second technique, namely, thiopentone, paralysing dose of relaxant followed by controlled respiration with nitrous oxide and oxygen, Flaxedil is not so satisfactory. In order to keep control of the respiration a very large initial dose of the drug is necessary, and, owing to the readiness with which diaphragmatic respiration returns, very frequent maintenance doses of Flaxedil are needed. Once spontaneous respiration has returned, relaxation soon becomes unsatisfactory in the upper abdomen if the patient is having only nitrous oxide and oxygen as the supplementary general anæsthetic. For the type of controlled respiration required for this technique, we find that tubocurarine is more suitable owing to its prolonged action in depressing the activity of the diaphragm and the more gradual wearing off of its relaxant effect.

If, at the end of an operation, relaxation for sewing up the peritoneum is insufficient, we would use a small dose of Flaxedil rather than tubocurarine as its effect is more immediate and wears off more rapidly.

Thoracotomies.—At this point it is convenient to mention the use of Flaxedil in thoracotomies because the same difficulties in maintaining control of respiration arise. If nitrous oxide and oxygen alone are used for the accompanying general anæsthetic, it is necessary to give a large initial dose of Flaxedil and very frequently repeated maintenance doses of the drug. Incidentally, as the heart is so readily visible to the surgeon, he may find that the tachycardia induced by large and repeated doses of Flaxedil is very disquieting.

Although our experience with Flaxedil in chest anæsthesia is small, we prefer the better control of respiration afforded by the longer-acting tubocurarine.

Cæsarean section.—Obstetric surgeons vary in their demands for relaxation in this operation. Some will find the already well-stretched recti no obstacle to their progress, while others demand relaxation sufficient to allow large packs to be placed between the intestines and the uterus. Whatever the surgical requirements, it is well recognized that the patient must be given the minimum of anæsthetic agents until the baby has been extracted. The maintenance of this light anæsthesia has been made easier and safer by the reflex depressant effect of a muscle relaxant.

When tubocurarine is used, its marked depressant effect on the intercostal muscles and the restriction of diaphragmatic movement by the gravid uterus very often make assisted respiration essential if maternal anoxia is to be avoided. In equivalent doses, Flaxedil does not paralyse the intercostals so markedly and assisted respiration is rarely needed. We therefore prefer to use it in Cæsarean section rather than tubocurarine, and give a dose of 60–80 mg. immediately after induction of anæsthesia.

External versions.—Another application of the effective but short-lived abdominal relaxant effect of Flaxedil is in the anæsthesia for external versions. Of all obstetric operations this is considered to require the most profound depth of anæsthesia. Some obstetricians would still like their patients to be given deep chloroform, while the majority regard ether to

the third or fourth plane as absolutely essential. We believe that, by the use of Flaxedil, the mother can be spared a deep general anæsthetic with its unpleasant sequelæ (Doughty, Hindle, MacDonagh, Sturton and Wylie, 1950).

In the majority of cases failure by the obstetrician to turn the baby without an anæsthetic is due to the mother's inability voluntarily to keep her abdominal muscles relaxed during the procedure. This difficulty can be overcome by giving her a small dose of thiopentone together with 60–80 mg. of Flaxedil. Anæsthesia is continued with nitrous oxide and oxygen. In most cases the uterine muscle will remain passive and allow the operator to turn the fœtus without opposition. In a smaller number of cases the uterus is irritable, particularly if the attempt at version is made after the thirty-sixth week of pregnancy. This irritable state may sometimes be appreciated by feeling the hard uterus through the mother's abdominal wall even before the induction of anæsthesia. In these circumstances, Flaxedil cannot be expected to relax the smooth muscle of the uterus and ether will have to be given. However, if anæsthesia is induced with a small dose of thiopentone and relaxation of the abdominal wall established with Flaxedil, it is quite surprising what a small amount of ether is required to relax the uterus. The mother is thus spared the soaking in ether which she would have had if no Flaxedil had been given.

Flaxedil in intubation.—The rapid establishment of an endotracheal anæsthetic has long been the goal of anæsthetists. During the last three years the use of muscle relaxants to facilitate intubation has become increasingly popular, though there are some quarters in which the method has not found favour.

We have attempted to make a clinical assessment of the relative merits of Flaxedil, tubocurarine and decamethonium in facilitating intubation. The ideal we aimed at was, first and foremost, to provide conditions in which an easy atraumatic intubation could be carried out. At the same time it was desirable that the dose of relaxant should not be such that the patient would require artificial respiration following intubation. The dose of thiopentone given with the relaxant was twice that required to send each patient to sleep. We classified each intubation into one of four groups according to the ease or difficulty of the intubation (Table I).

These figures show that with a dose of Flaxedil of lower curarizing potency than the dose of decamethonium or tubocurarine, the highest percentage of easy intubations was achieved.

Table I also shows the number of cases requiring artificial respiration of those in whom an easy intubation was carried out.

These figures suggest that Flaxedil is the most suitable drug of the three in establishing endotracheal anæsthesia. Of course better results would be obtained with all three drugs by varying the amounts of thiopentone and relaxant used in the light of one's experience of the method. But in order to make a fair comparison, we had to adhere to a fixed standard of dosage (Doughty, 1950; Doughty, Hindle, MacDonagh, Sturton and Wylie, 1950).

Bronchoscopy.—The insertion of a bronchoscope is but a step away from laryngeal intubation, yet there are many difficulties in providing a satisfactory general anæsthetic for it. From the surgeon's point of view an efficient topical analgesia may be the most satisfactory contribution that the anæsthetist can make, as the conscious patient can, to a certain extent, control his coughing. From the patient's point of view both the application of the "local" and the bronchoscopy itself must be a very unpleasant experience, so, if adequate conditions for the surgeon can be provided, a general anæsthetic has obvious advantages.

Our experience with Flaxedil in facilitating intubation can be applied to anæsthesia for bronchoscopies. Here it is of particular importance that the passage of the bronchoscope should be easy and that artificial respiration during the bronchoscopy should not be necessary.

We have had very satisfactory results by inducing anæsthesia with thiopentone and Flaxedil, followed by a thorough application of cocaine or amethocaine to the larynx, trachea and carina by means of the Macintosh spray. Any tendency to cough during the bronchoscopy can be checked by further small injections of a Flaxedil-thiopentone mixture.

By this means we have been able to anæsthetize for bronchoscopies without the anxiety occasioned by inadequate respiration if tubocurarine is used as the relaxant. With Flaxedil the cough reflex is depressed without seriously interfering with respiratory efficiency.

Recently we have found that an intravenous injection of 25 mg. of pethidine given immediately before induction of anæsthesia seems to increase the tolerance of the bronchoscope by the patient and less thiopentone and Flaxedil seem to be required for maintenance.

II

The second main property of Flaxedil is its effective but short period of action. This brings us to a group of circumstances in which this property is utilized.

For instance, for œsophagoscopies the anæsthetic requirements are a clear airway and relaxation of the cricopharyngeus muscle. The clear airway is ensured by intubation under thiopentone and Flaxedil. The relaxation of the cricopharyngeus due to the Flaxedil is transitory, but it lasts long enough provided the surgeon is ready to pass the œsophagoscope as soon as the patient has been intubated.

Hæmorrhoidectomies and sigmoidoscopies are short but notoriously stimulating operations normally requiring quite deep anæsthesia. They may now be carried out quite safely under light anæsthesia using Flaxedil as a depressant of the reflexes and as a temporary relaxant of the anal sphincter.

The reflex depressant effect of Flaxedil can be used in the treatment of persistent or recurrent laryngeal spasm. Quite a small dose, say 20 to 40 mg., will relax the vocal cords and enable the anæsthetic to proceed smoothly. This spasmolytic effect of Flaxedil is particularly useful when one is teaching a student to give ether to a resistant patient. There comes a time when one's duty to the patient and the waiting surgeon overrides one's teaching obligations to the student. On such an occasion a syringe of Flaxedil is more elegant in use and less traumatic than a boxwood wedge, a Mason's gag and a tongue forceps.

Flaxedil may find a place in the production of relaxation for orthopædic manipulations and reductions of dislocations. The most commonly used anæsthetic for this purpose is intravenous thiopentone given rapidly. The surgeon insists on a rapid injection of the thiopentone as he knows that adequate relaxation does not last much longer than the period of apnœa. Anæsthetists who have had experience of sudden and unexpected circulatory collapses following the rapid injection of quite moderate doses of thiopentone will find that a thiopentone-Flaxedil mixture injected slowly is safer and provides less transient relaxation. The mixture used is 0·5 gramme of thiopentone with 40 mg. of Flaxedil. This is injected slowly until a little more than the sleep dose has been given. The operator must be restrained for about a minute and a half in order to allow the Flaxedil to work. In most cases sufficient relaxation will be obtained for a manipulation of the back or for reduction of a dislocated hip or shoulder without subjecting the patient to the risk of a large dose of barbiturate.

III

The third important characteristic of Flaxedil is that neostigmine appears to be a more effective antidote to its action than to tubocurarine. We will now indicate two different circumstances in which it is considered justifiable to paralyse a patient with Flaxedil and to hasten his recovery from the drug by means of neostigmine.

Electro-convulsive therapy.—In electro-convulsive therapy, a muscle relaxant is commonly used in small doses in order to soften the intensity of the induced convulsion. In the clinic in which we have worked it is not the practice to give an anæsthetic or a relaxant to every patient, as it is believed that a full unmodified convulsion has the best therapeutic effect. But we have been asked to render patients almost completely immobile when the current is passed if there is a danger that an existing disability would be aggravated by a convulsion. Examples of this type of patient include those with severe hypertension or coronary disease and those suffering from severe osteoarthritis or convalescent from recent fractures or orthopædic operations. The production of immobility in these cases involves the use of doses of Flaxedil considerably greater than in those in which it would be given merely to soften the effect of the convulsion.

Our patients are premedicated with atropine and are given a dose of thiopentone just sufficient to send them to sleep. Flaxedil is then injected in doses of about 160 mg. for a large man to 120 mg. for a woman. Oxygen is given for a minute and a half while the Flaxedil is exerting its effect. The current is passed and the only movement of the patient is a twitch of the facial muscles. The clonic phase follows and is manifested by regular movements of the facial muscles and sometimes by a shrugging motion of the shoulders. After the clonic phase the lungs are gently inflated with oxygen for about a minute, by which time the patient usually begins to make some respiratory effort. This period of apnœa normally follows a convulsion unmodified by a muscle relaxant. It is quite remarkable that respiration should start so promptly after such large doses of Flaxedil, but this is believed to be due to the large amount of acetylcholine which must be liberated at the neuromuscular junction at the time of the convulsion.

Neostigmine with atropine is injected intravenously—at first 2·5 mg. neostigmine and 1/100 gr. (0·65 mg.) atropine—and the effect observed. This is followed by a further smaller dose if the intercostal respiration appears to be inadequate after the first injection. During the procedure a Boyle's machine with oxygen, laryngoscope and endotracheal tubes is kept ready at hand but in our experience laryngeal intubation has never been necessary.

Angiocardiography.—Another occasion on which it is considered justifiable to paralyse a patient with Flaxedil and to abolish its effect by means of neostigmine is in angiocardiography. This is a radiological investigation of a patient with cyanotic congenital heart disease on whom an operation of the Pott's or Blalock type is contemplated. A radio-opaque solution—diodone—is injected into an antecubital vein and its course through the heart and great vessels followed by a series of twelve X-ray exposures taken in very rapid succession. The surgeon can then determine the operability of the congenital lesion and which particular operation is practicable.

For the accurate interpretation of the angiocardiogram it is essential that perfect X-ray pictures are taken and this is only possible if the patient is kept absolutely still during the exposures. The conscious patient cannot be relied upon to keep still and hold his breath, as the injected solution produces very unpleasant sensations. Under light anæsthesia the injected solution causes coughing and laryngeal spasm. The alternatives that remain are anæsthesia to respiratory arrest with cyclopropane or ether, or light anæsthesia with neuromuscular paralysis. On account of the explosion risk in an X-ray department, we prefer the latter method and accelerate recovery from the paralysing dose of Flaxedil by means of neostigmine and atropine.

At first it may seem rather drastic completely to paralyse a patient for an X-ray examination and to use what might be a dangerous drug as an antidote, but it is felt that the importance to the patient of accurate assessment of his operability outweighs the possible risk of the anæsthetic procedure.

Use of neostigmine.—The disadvantage of neostigmine is that in addition to reversing the muscle-paralysing action of the curarizing drugs, it causes salivary and bronchial secretion, intestinal spasm and other effects of parasympathetic stimulation. Among these is the dangerous depression of the heart due to vagal stimulation. Strong vagal stimulation need not necessarily cause death, for the heart may start beating again by virtue of the vagal escape phenomenon even in the presence of continued stimulation of the vagus. The impulses which re-start the heart are thought to arise from some level in the junctional tissue below the sino-auricular node. However, if the junctional tissues are depressed as by cyclopropane or if the heart muscle is in poor condition, it is reasonable to suppose that the heart may not be able to escape from the inhibitory influence of the vagus and will remain arrested.

Another factor which may play a part in the risk of death following neostigmine is that its effect in slowing the heart-rate may be enhanced by the direct action of cyclopropane in depressing the activity of the sino-auricular node.

The patient may be protected to a certain extent from the vagal effects of neostigmine by atropine or a similar drug given as premedication, and by atropine given with or before the injection of neostigmine. The customary dose is 1/100 (0·65 mg.) to 1/75 (0·9 mg.) grain with each 2·5 mg. of neostigmine, though one should remember that it is necessary to give 1/20 (3·2 mg.) to 1/15 (4·3 mg.) grain to produce complete vagal block in the average adult. It should not be forgotten that both tubocurarine and Flaxedil have some vagal blocking activity which may contribute to the protection afforded by the atropine.

In 1949 three deaths following neostigmine were reported in the *British Medical Journal* (Macintosh; Clutton-Brock; Hill). Two of these cases were associated with cyclopropane anæsthesia. In one case necropsy showed "a very poor myocardium". In the other the heart was said to be "dilated" and was associated with a very severe peritonitis due to a gangrenous appendix. This patient may well have had some degree of toxic myocarditis which rendered his heart unable to withstand the depressant effect of neostigmine combined with cyclopropane. The third death following neostigmine was a baby who was given a very large dose in circumstances in which it would appear from the report that its use was not indicated at all.

It follows, then, that neostigmine should be used with caution and only when genuinely needed, as for instance when the anæsthetist is faced with the problem of an apnœic patient at the end of an abdominal or thoracic operation. Here, there is usually an element of both medullary and neuromuscular depression, neither of which by itself would be sufficient to cause apnœa. Thiopentone, cyclopropane, acapnia due to hyperventilation with carbon dioxide absorption, and pethidine may all contribute to the medullary element of respiratory depression.

It is therefore logical and safer to eliminate the medullary depression before giving neostigmine. The carbon dioxide absorber should be disconnected and the patient ventilated with nitrous oxide and oxygen to expel cyclopropane, which we have already seen is an undesirable associate for neostigmine. If apnœa continues, an adequate dose of a safe respiratory stimulant such as 5 c.c. of nikethamide should be given intravenously.

When respiration starts one can judge from its character whether an injection of neostigmine is necessary. After the abolition of medullary respiratory depression, only a comparatively small dose may be needed to restore the activity of the intercostal muscles.

We use neostigmine without hesitation when respiratory depression is due mainly to curarization. We attempt to reduce to a minimum the occasions on which it must be used, by giving the patient the smallest effective dose of relaxant. We always give atropine with neostigmine, and always eliminate cyclopropane from the patient before the injection.

IV

The fourth main property of Flaxedil is that it does not cause a lowering of the blood pressure.

Tubocurarine, in common with other drugs which block the sympathetic ganglia, causes a fall in blood pressure which is usually negligible in normal subjects but is often very marked in the hypertensive. Flaxedil does not block the sympathetic ganglia so that a patient's blood pressure is maintained at a higher level under anæsthesia than after tubocurarine.

This difference between tubocurarine and Flaxedil is probably of little significance when dealing with normal patients, but with the elderly hypertensive arteriosclerotic patient undergoing a severe operation, it is desirable to preserve what little resilience is left in the peripheral arterioles by doing nothing to interrupt their sympathetic nervous control. An additional risk in this type of patient is that a period of undue hypotension may predispose to a cerebral or a coronary thrombosis.

In this connexion we have in mind 8 patients who were recently anæsthetized for retropubic prostatectomy. The youngest was 72, and 2 were 85. They were given a small dose of thiopentone as induction, 80–120 mg. of Flaxedil for relaxation and anæsthesia was maintained with nitrous oxide and oxygen. A blood transfusion was set up before the start of the operation so that blood could be replaced as soon as it was lost from the operation site.

Fig. 6 shows the chart of the last one and demonstrates the high blood pressure being maintained after the induction of anæsthesia and the excellent response made by the patient to blood transfusion following a brisk hæmorrhage.

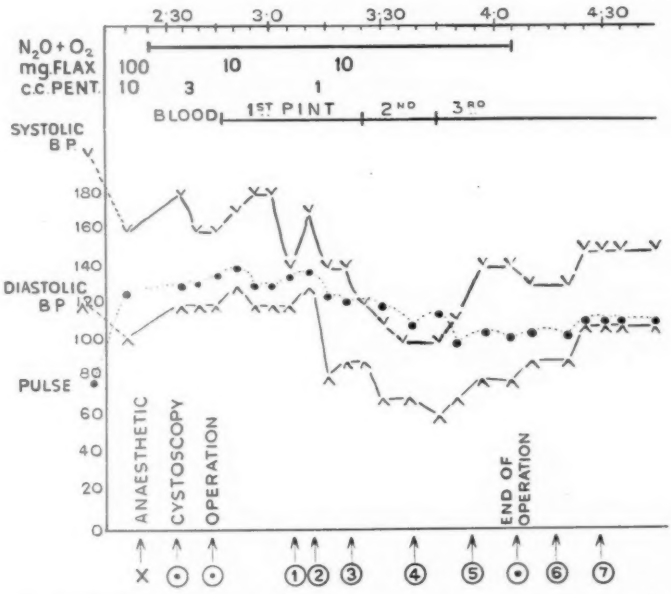


FIG. 6.—1.—Enucleating prostate. 2.—Hæmorrhage. Blood drip speeded up. 3.—Straining. More Flaxedil given. Hæmorrhage continues. 4.—Constant hæmorrhage. 5.—Hæmorrhage stopped. Sewing up. 6.—In the ward. 7.—Conscious.

These conclusions are drawn from only a few cases, but the operative and post-operative condition of the patients has been very gratifying; we therefore feel that it is worth recording this use of Flaxedil in helping to maintain an elderly hypertensive's blood pressure during an operation, especially at a time when so much interest is directed towards drugs having precisely the opposite effect.

Conclusions

This assessment of Flaxedil illustrates that it is a very versatile and safe muscle relaxant. The fact that it is a short-acting curarizing agent with an effective antidote has widened the field of application for this type of drug in clinical anæsthesia.

Its short period of action is not only one of its main advantages but it is at the same time its main limitation. Though it *can* be used for prolonged relaxation and for control of respiration if frequently repeated injections are given, the longer-acting tubocurarine seems to be more suited to these purposes.

Flaxedil's one main disadvantage—tachycardia—has been observed in many patients under thiopentone, nitrous oxide and oxygen anæsthesia, but not to the same extent under cyclopropane. Though the rapid pulse may be disquieting to the anæsthetist, and may, in theory, mask danger signals of the patient's general condition, we have been unable to attribute to tachycardia any undesirable effects on our patients.

We should like to express our thanks to those colleagues at St. Thomas's Hospital and at the Kingston Group of Hospitals who helped in much of the work, to W. Hindle, B.Sc., who carried out most of the experiments, and to Messrs. May and Baker Ltd. for generous supplies of Flaxedil.

References

Bovet, D., Depierre, F., and de Lestrange, Y. (1947) *C.R. Acad. Sci., Paris*, **223**, 597.
Clutton-Brock, J. (1949) *Brit. med. J.* (i), 1007.
Dos Santos, J. C., and Soares, E. L. (1950) *Gaz. méd. port.*, **1**, 155.
Doughty, A. G. (1950) *Lancet* (i), 899.
——, Hindle, W., MacDonagh, P. F. M., Sturton, R. V., and Wylie, W. D. (1950) *St. Thom. Hosp. Rep.*, **6**, 208.
Hill, M. (1949) *Brit. med. J.* (ii), 601.
Jacob, J., and Depierre, F. (1950) *Arch. int. Pharmacodyn.*, **83**, 1.
Macintosh, R. R. (1949) *Brit. med. J.* (i), 852.
Mushin, W. W., Wien, R., Mason, D. F. J., and Langston, G. T. (1949) *Lancet* (i), 726.
Paton, W. D. M., and Zaimis, E. J. (1950) *Lancet* (ii), 568.
Wien, R. (1950) Personal communication.
Wilson, H. B., and Gordon, H. E. (1949) *Lancet* (ii), 504.

Dr. R. Wien: *Flaxedil tachycardia.*—Tachycardia with Flaxedil is not readily observed experimentally unless dogs, which have a high degree of vagal tone, are used. Under certain conditions, however, Flaxedil does cause an increase in the heart-rate in dogs, but not in cats or rabbits where the pulse is already high and the vagal tone comparatively low.

In dogs premedicated with morphine to stimulate the vagal centre and then anæsthetized with thiopentone, tachycardia was consistently observed following the intravenous injection of Flaxedil in a dose of 0·2–0·4 mg./kg., which is just below that required for a complete neuromuscular block. There was an increase in the heart-rate (120–176 per minute) of $20 \pm 3{\cdot}7\%$ (mean of 6 experiments), and the effect persisted for about ten to sixty minutes. Tubocurarine in an equipotent curarizing dose of 0·05–0·1 mg./kg. similarly caused tachycardia, but the effect was very transient, lasting only three to five minutes.

After vagal tone had been abolished with either atropine or hexamethonium (drugs which themselves caused an increase in the heart-rate) Flaxedil did not then cause any further increase in the rate, which suggests that there was no direct effect on the heart. This supposition was confirmed by observations in the spinal dog, where the vagal centre is destroyed; in this preparation Flaxedil did not cause a tachycardia. Moreover there was no rise in blood pressure, which would have occurred had there been any stimulant action on the sympathetic nervous system.

Tachycardia observed clinically can be accounted for by an action on the extrinsic nerves controlling the heart: this might consist of an effect on the parasympathetic and sympathetic systems. Though no evidence was found for a stimulant action on the sympathetic system, in equipotent doses causing neuromuscular block Flaxedil had a greater effect than *d*-tubocurarine in reducing the fall of blood pressure on vagal stimulation. In support of this evidence of an inhibitory action on the vagus nerves, it was found that Flaxedil had a weak anti-acetylcholine or atropine-like action, though only

about 1/500th of the potency of atropine itself. The partial removal of vagal control most probably accounts, therefore, for the tachycardia observed. This explanation is supported by other observations of Bovet *et al.* (1949), Unna *et al.* (1950) and Jacob and Depierre (1950).

Tubocurarine produces a much less marked and very much more transient tachycardia in dogs, and the absence of such an effect in patients might be explained by the comparatively greater inhibitory effect of this compound on the sympathetic and smaller effect on the parasympathetic system. In those circumstances where the vagal tone is sufficiently low or is abolished by the previous administration of atropine or scopolamine, the administration of Flaxedil should have no effect on the frequency of the heart-rate.

The practical implications of these findings are that some subjects may normally show a tachycardia with Flaxedil, which should not be confused with that due to other causes indicative of some upset of the anæsthesia or operation. The appearance of tachycardia will depend on the degree of vagal tone existing in the particular individual as well as on the type of anæsthetic, the depth of anæsthesia, and on the use of drugs such as morphine and atropine for premedication.

REFERENCES

BOVET, D., DEPIERRE, F., COURVOISIER, S., and DE LESTRANGE, Y. (1949) *Arch. int. Pharmacodyn.*, **80**, 172.

JACOB, J., and DEPIERRE, F. (1950) *Arch. int. Pharmacodyn.*, **83**, 1.

UNNA, K. R., PELIKAN, E. W., MACFARLANE, D. W., and SADOVE, M. S. (1950) *J. Pharmacol.*, **100**, 201.

Dr. L. Rendell-Baker (Department of Anæsthetics, Cardiff): The original experimental and clinical investigation of Flaxedil was carried out in the Department of Anæsthetics at Cardiff in 1949. Since then Flaxedil has been used instead of tubocurarine with equally satisfactory results.

Tachycardia has been noted, but has never given rise to any anxiety, though Flaxedil has been used in many cardiac operations and other poor risk cases. The difference between tubarine and Flaxedil can best be illustrated by some personal experiences during the experiments with Flaxedil. There were insufficient people in the Department to carry out a number of experiments on volunteers at one session, without also utilizing the volunteers as observers for subsequent experiments. Such was the speed of recovery from Flaxedil, however, and so few were the after-effects, following a suitable dose of prostigmine and atropine, that within five minutes of the termination of one experiment, the "experimental animal" was able to co-operate fully in the next. One afternoon after having Flaxedil, I drove home with another volunteer who had received tubocurarine. The contrast between us was most marked: I was able to drive with confidence, whereas my passenger was limp and unable to focus his vision clearly owing to diplopia. The effect of prostigmine on the bowel, in spite of the addition of atropine, was most marked, and this colic proved to be the most troublesome sequel to the experiment.

We feel it is most undesirable that a patient should be sent back to the ward before regaining full muscular power. It is almost a routine in our Department to give a suitable dose of prostigmine, preceded by atropine, to patients who have had Flaxedil. The degree of bradycardia which follows the administration of prostigmine, if the atropine has not had sufficient time to act, is most marked, and as a result we now inject the atropine intravenously fifteen to twenty minutes before the injection of prostigmine.

Flaxedil produces excellent operating conditions in thoracic surgery, provided the nitrous oxide anæsthesia is supplemented with small doses of pethidine, and I think that the inadequate depth of the accompanying anæsthesia was the reason for Dr. Doughty's having to use such large doses of Flaxedil.

Dr. J. G. Bourne: I disagree with my colleagues who prefer Flaxedil to C.10 (decamethonium iodide) to facilitate intubation. For two or three years I used "Tubarine" for this purpose in "steam hammer doses" and I had no trouble. However, when Flaxedil and C.10 became available it was clear that the shortness of their action was an advantage. Of these two relaxants I prefer C.10 since, unlike Flaxedil, its action is free from side-effects. It is also more transient.

In comparing the facility offered by these three relaxants for intubating, Dr. Doughty put C.10 lowest as making intubation "easy" in only 60% of cases. With this figure I disagree. Intubation is easy in 100% of cases if pentothal and C.10 are given in correct dosage. The dose can be computed as follows: The two drugs are mixed in solution so that 20 millilitres contains 1 gramme of pentothal and 5 mg. of C.10. The patient is weighed in pounds. 10% of this weight represents the number of millilitres to be injected intravenously. With this dosage intubation is easy in every case, and at worst all that is needed is manual compression of the bag for five minutes, a procedure which is nowadays a reflex with every anæsthetist.

Experience with this dosage in 200 consecutive cases of tonsillectomy in children aged 4 to 14 has illustrated both the usefulness of C.10 for intubating and its transient action. In this series the average time taken per case from the moment of injecting the drugs to the completion of the operation has been fifteen and a half minutes, anæsthesia being maintained with nitrous oxide-oxygen. In every case intubation has been easy, and in no case has it been necessary to use oxygen, artificial respiration or any restorative at the end of the operation. There have been no complications due to the anæsthetic.

Facilitation in intubation constitutes practically the sole indication for the use of C.10 in anæsthesia.

At least two or three minutes should be given for its full effect to develop, and during this interval the patient's lungs should be rhythmically inflated with oxygen.

Dr. William W. Mushin: Apart from the production of tachycardia there is very little obvious clinical difference between the effects of Flaxedil and those of *d*-tubocurarine. In fact I think it would be fairly safe to challenge anyone to walk into an operating theatre during an anæsthetic and to say which of the two relaxants was being used. My own reasons for continuing to use Flaxedil at Cardiff are based more on patriotism than on pharmacology. In Flaxedil we have a comparatively cheap and easily produced near-perfect substitute for *d*-tubocurarine and in any future emergency we would not have the previous difficulty of obtaining the natural substances from a distance of many thousand miles. Apart from the question of cost, availability and the tachycardia, I see little real clinical reason for using one rather than the other.

Dr. Doughty (in reply): I agree with Dr. Rendell-Baker that Flaxedil and nitrous oxide and oxygen will provide excellent conditions for control of respiration, if combined with small doses of pethidine, or for that matter any anæsthetic or analgesic more potent than nitrous oxide. I deliberately avoided mentioning the use of pethidine for this purpose since I was concerned with comparing Flaxedil and tubocurarine under comparable conditions. Owing to its more prolonged action and less diaphragm-sparing effect, tubocurarine provides better control of respiration than Flaxedil, when used with nitrous oxide and oxygen alone. I think this observation serves to underline one of the essential differences between the two drugs.

With regard to our contention that Flaxedil is the most suitable relaxant for facilitating intubation, I agree with Dr. Bourne and other speakers that other relaxants may be adequate for this purpose, if the dose of thiopentone given at the same time is varied according to one's experience of the method. We gave a fixed *small* amount of thiopentone, i.e. twice the sleep dose, in order to ensure that the conditions provided for intubation were due more to the relaxant than to the barbiturate. Larger doses of thiopentone would ensure an easier intubation, but, as Dr. Bourne admits, would result in a period of apnœa necessitating artificial respiration. If the ideal aimed at is an easy intubation followed by spontaneous respiration, the results we obtained with Flaxedil approached the ideal more closely than with tubocurarine or decamethonium.

Section of Comparative Medicine

President—Professor A. HADDOW, M.D., D.Sc., Ph.D.

[*December* 20, 1950]

The Macromolecular Structure of Keratin Fibres

By P. ALEXANDER, Ph.D., D.I.C., A.R.C.S.

Chester Beatty Research Institute, The Royal Cancer Hospital; and the Department of Inorganic and Physical Chemistry, Imperial College, London

ALTHOUGH there are profound morphological differences between the different types of keratin fibres, Astbury and Woods (1933) showed that there was a unity in their macromolecular structure. Wool has been studied in much greater detail than any other keratin fibre and in this paper this fibre only will be considered, although there can be little doubt that the conclusions can be extended to keratin fibres in general. The insolubility of keratin makes a detailed study of its macromolecular structure almost impossible, and it has been realized for a considerable time that this results from the presence of disulphide crosslinks. Although many attempts have been made to solubilize keratin none of these is suitable for studying its macromolecular structure, since either breakdown of the main peptide chain takes place or only a small part of the material is rendered soluble.

Toennies and Homiller (1942) showed that performic acid, though a very powerful oxidizing agent, did not oxidize the NH_2 group in amino acids and only oxidized the side chains of tryptophane, methionine and cystine—the latter to cysteic acid. Sanger (1950) made use of this reagent to split the disulphide bond in insulin and in this way resolved this protein into a number of polypeptides. It is desirable to treat keratin in aqueous solution so as to ensure that all parts of the fibre are accessible, and performic acid cannot be used in this way since it decomposes into carbon dioxide and water under these conditions.

Separation of wool into three fractions.—We found that peracetic acid is stable for many days even in very dilute aqueous solution and that the rate of establishment of the equilibrium $CH_3COOOH + H_2O \rightleftharpoons CH_3COOH + H_2O_2$, though rapid when forming peracetic acid, is very slow in the reverse direction. Peracetic acid was shown to be as specific as performic acid in its reaction with amino acids (Alexander, Hudson and Fox, 1950). Recent experiments with a large range of di, tri, and penta peptides, including those containing cystine and tryptophane, which were relatively easily prepared by a new synthesis (Bailey, 1950), showed that peracetic acid did not break peptide bonds even when it oxidized the side chain of one of the amino acids. We find that peracetic acid readily oxidized all the disulphide bonds in wool and that no sulphur was lost in this reaction. This reagent is therefore suitable for solubilizing wool, since it seems almost certain that the products thus obtained have not undergone any main chain degradation. Until more than 80% of the disulphide bonds have been broken with peracetic acid only about 8% of the oxidized wool is soluble in dilute ammonia, but when all these have been severed between 90 to 92% of the wool goes readily into solution (Alexander, Fox and Hudson, 1951).

The insoluble residue of between 8 to 10% consists of a membrane (Alexander and Earland, 1950*a*) which in spite of the complete absence of disulphide bonds is insoluble in cupriethylene diamine, strong solution of lithium bromide and only dissolves slowly with degradation in N sodium hydroxide and concentrated hydrochloric acid. This insoluble membrane was shown to be the subcuticle which was predicted by Reumuth and shown by Zahn and Haselmann (1950) to form the outer layer of the cortex below the scales. This insoluble residue gives an X-ray photograph typical of unoriented β keratin (Alexander, Earland and Happey, 1950) and infra-red studies carried out by Dr. A. Elliott confirm that it is not an

α protein. The subcuticle membrane probably exists in the unoriented β phase in the fibre since the oxidation by peracetic acid does not change the X-ray photograph of the whole fibre (Alexander, 1951).

From the ammoniacal solution of the peracetic acid treated wool 60% of the dissolved protein can be precipitated by the addition of mineral acid to give a pH<3 or by concentrated electrolyte. This material can readily be redissolved in dilute ammonia or, if the acid groups have been neutralized, in water, and will be referred to as α *keratose*. It gives an X-ray diagram typical of α keratin and can be spun into a fibre which gives an X-ray diffraction pattern almost indistinguishable from native wool.

A physical chemical investigation by Drs. B. E. Conway and L. Gilbert which will be reported in detail elsewhere shows that the α keratose gives an electrophoretic pattern consisting mainly of one peak together with some ill-defined band. The material giving rise to the latter can readily be removed by fractional precipitation and a substance is left which is electrophoretically homogeneous. This major component of α keratose was shown to have a molecular weight of 70,000 and to consist of particles which are completely spherical. The low molecular material which is not precipitated on acidification (approx. 35% of the fibre as a whole) is polydisperse and has an average molecular weight of 4,500. It is in the β configuration and will be referred to as γ keratose. The amino-acid composition of the three components of the wool fibre are significantly different. The most important variation is in the sulphur content of the α and γ fractions which contain respectively 1·6% and 6% of sulphur.

Elöd and Zahn (1949) found that wool fibres in which the disulphide bonds had been reduced with thioglycollic acid super-contracted under very mild conditions, and that such fibres could be brought into the disoriented β configuration (*d* keratin) by treatments which do not change native wool. We found (Alexander, 1951) that oxidation of the disulphide bond led to the same instability. After a treatment in which all the cystine had been oxidized fibres gave the same X-ray picture as untreated wool, confirming the deduction of Astbury and Woods (1933) that the disulphide bond does not enter into the crystalline spacings of wool. The oxidized fibre, however, contracts on being placed for a few minutes into water at 95° C. or into formic acid, followed by washing with water, and then gives an X-ray picture of disoriented β keratin. Neither of these treatments of course affects in any way the structure of native (i.e. disulphide crosslinked) wool.

The soluble α keratose when precipitated as a powder undergoes the same crystalline changes as the oxidized fibres, and the α fold is changed into the β fold by dry heat at 110° C. (the α fold in native wool is stable up to 170° C.) and by water at 95° C. in five minutes. α keratose, which is soluble in hydrogen bond-breaking solvents, dissolves readily in anhydrous formic acid from which it is precipitated in the α fold on adding water, but if the acid is distilled off under vacuum (40° C.) the keratose left is in the β configuration. Reactions which degrade the molecule by the breaking of peptide bonds bring about conversion into the β configuration. It can therefore be concluded that a soluble globular protein-like molecule can exist in the α fold but in the absence of stabilizing crosslinks is converted into the β form by treatments known to produce denaturation. The keratose when converted into the β form by a process which does not degrade the protein exhibits much greater intermolecular attraction than in the α configuration. Because of this the β form dissolves much less readily, and frequently a sample will not have dissolved completely even after several days in ammonia, unlike the α keratose which only requires a few hours under the same conditions; also the β form swells much less in water and phenol. When the α keratose is converted into the β configuration the molecules are no longer spherical but exhibit a very pronounced asymmetry, and must be considered as rods. Probably the molecule in the β configuration is held in fixed folds by hydrogen bonds and cannot coil up at random as in the α fold.

All these findings can readily be interpreted in terms of the molecular structures originally proposed by Zahn (1947) and now also assigned by Ambrose and Hanby (1949) on the basis of infra-red spectra to the α fold. In this fold all the possible hydrogen bonds of the peptide link are taken up in maintaining the α fold, but become available for interchain crosslinks in the β fold. Strong additional support for this model is provided by the observation (Bamford, Hanby and Happey, 1951) that certain synthetic polypeptides exist in the α form when they are soluble in benzene, but can be converted into the β form by treatment with formic acid when they become insoluble. The interchain hydrogen bonding seems in general to confer insolubility in non-hydrogen bond breaking solvents on β proteins and the limited solubility of the keratose when in the β form is probably due to the sulphonic acid groups introduced by the oxidation.

The role of hydrogen bonds in the structure.—Although many workers and notably Astbury (1940) had appreciated the importance of hydrogen bonds in the structure of wool,

Elöd and Zahn (1947) were the first to show in a series of notable papers that by breaking secondary valency bonds only with formamide and phenols wool fibres contracted, underwent changes in their crystalline structure and were rendered almost wholly digestible by enzymes. They concluded that the forces holding the molecules together were due to hydrogen bonding and that the disulphide bond had a subordinated part in the crystalline areas and exercised its influence largely in the intermicellar phase. The reagents used by Elöd and Zahn are powerfully adsorbed by wool and bring about great lateral swelling at room temperatures, but supercontraction only occurs at elevated temperatures and is irreversible.

Phenol is not a potent hydrogen bond breaker (e.g. it does not dissolve silk). Its effect on the fibre is complicated and the role of hydrogen bonds in the macromolecular structure of wool can more readily be studied (Alexander, 1951) with strong solutions of lithium salts which act on the fibre in the cold in a completely reversible manner, and which dissolve silk without degradation. When a dry wool fibre is immersed in a solution of 75 grammes of lithium bromide in 100 grammes of water it swells slowly (if a wet fibre is used the first and rapid action of the lithium bromide is to desiccate it by an osmotic effect), becomes progressively weaker, and after about twenty hours at 20° C. contracts by approximately 15%. When removed from the salt solution and placed into water it fully regains its original length and strength. The time necessary for contraction is considerably less at higher temperatures. The gradual swelling and supercontraction of wool occurs only in concentrated solutions of lithium salts (i.e. more than 50 grammes LiBr in 100 ml. solution) and solutions of equivalent strength of, for example, potassium or magnesium chloride have no effect. It is suggested that the breaking of hydrogen bonds in these solutions is due to the high polarizing power of the incompletely hydrated lithium ion which associates with polar groups in the wool and prevents them from forming hydrogen bonds. Speakman (1947) found that fibres no longer supercontract in bisulphite when their disulphide bonds had been replaced by more stable crosslinks. Such modifications, however, do not influence the contraction of fibres in lithium bromide solution. It is found that concentrated solutions of lithium bromide are capable of reversing the so-called permanent set obtained by holding a fibre stretched in steam, but they are not capable of reversing the set obtained by reducing disulphide bonds and rebuilding them in the stressed fibre. The action of the lithium bromide on the fibre always brings with it disorientation of the crystalline areas and the α X-ray photograph is changed into a disoriented β pattern.

When more than 90% of the disulphide bonds have been broken with peracetic acid the fibre supercontracts without any change in X-ray picture taking place, and this contraction is prevented when the disulphide bonds are replaced by more stable links. From these investigations it was concluded that decrease in elasticity, permanent set and supercontraction can all be brought about by reactions involving either the disulphide bond, as pictured by Speakman (1947), or by breaking hydrogen bonds, as suggested by Elöd and Zahn (1947). The latter mechanism is characterized by changes in the crystalline phase, whereas after physical changes resulting from reactions involving the disulphide bond only the crystalline arrangement remains the same. We concluded (Alexander, 1951) that these facts could be interpreted if it is assumed that the fibre is made up of micelles, which are joined to one another via disulphide crosslinks, but that the molecules within the micelles are held by secondary valency forces only, although they may contain two-dimensional cystine links.

The macromolecular structure.—The model derived from the above consideration receives direct support from fractionation of oxidized wool into a high molecular weight fraction of high cystine content (Alexander, Earland and Happey, 1950). It can be concluded that the micelles are made up of polypeptide chains of molecular weight 70,000 and crosslinked in two dimensions by disulphide bonds, but held in position by hydrogen bonds. These molecules are normally in the α fold and the micelles contain some crystalline areas but are probably not wholly crystalline. The micelles are surrounded by a cement consisting of low molecular weight polypeptide chains which are very rich in cystine. The cement is bonded three dimensionally by disulphide crosslinks which also probably link it chemically to the molecules in the micelles. An X-ray photograph of this cement after oxidation of the disulphide bonds shows it to be in the β configuration. As there are no crystalline areas in the cement this β phase cannot be detected by means of X-rays, but infra-red investigations on decuticulated hair (Ambrose and Elliott, 1951) indicate the presence of a small proportion of protein in the β configuration; it is suggested that this material is the cement.

According to this model it is possible to obtain supercontraction in two ways: (1) by breaking the disulphide bonds in the cement, the molecules of which then coil up as in rubber (i.e. temperature increase facilitates contraction) and pull the micelles closer together, without however changing their crystalline shape; (2) by breaking the hydrogen bonds within the molecules of the micelles which then coil up, and fibre-shortening occurs with disorientation

in the crystalline phase. Similarly a fibre can be set in an extended form by breaking the disulphide bonds in the cement and reforming them when the fibre has been stretched or by changes within the micelles, with consequent alteration in the X-ray photograph. On stretching a fibre the α fold is opened up and elongation is the result of molecular unfolding to the β configuration. From X-ray pictures it is seen that the change from α to β is perceptible after 30% and virtually complete after 60% extension. Elöd and Zahn (1947) showed that fibres whose disulphide bonds had been reduced showed the α to β conversion after much higher extensions only. We have observed the same effect in fibres where the disulphide bond has been oxidized, in which the conversion of α to β is not complete even after an extension of 130% (reversible). Reference has already been made to the stabilizing influence of disulphide bonds on the α fold, and it is probable that the 5% of cystine in the high molecular fraction (i.e. the micellar material) contributes to the stability of the α fold in wool.

In their classical paper Astbury and Woods (1933) suggest, on the basis of mechanical evidence, that the morphological cells of the wool fibre consist of three phases, a micelle and intermicellar cement and a tough skin surrounding the micelles. Direct chemical support for this picture is provided by the chemical separation of wool into three fractions, described in this paper. The only modification which has to be made in the Astbury and Woods' picture is that the tough skin does not surround each individual micelle but the whole cortex of the fibre.

The X-ray data for this paper was provided by Dr. F. Happey and will be published in detail later.

Summary

(1) On oxidizing the disulphide bond with peracetic acid 90% of the wool fibre can be brought into solution without main-chain degradation. The soluble portion consists essentially of two components; α keratose of molecular weight approx. 70,000 and γ keratose with an average molecular weight of 4,500.

(2) α keratose gives an X-ray picture typical of proteins in the α fold and can be made into a fibre whose X-ray photo is almost identical with that of native wool. In solution the α keratin exists as a spherical molecule. γ keratose is in the β configuration. The α fold is shown to be much less stable in these preparations than in a native wool fibre and it is concluded that the disulphide bonds contribute materially to the stability of the α fold.

(3) It is shown that the α keratose can be converted into a protein giving a β X-ray picture and that in this form it is much less soluble and when in solution the molecules are no longer spherical. The structure for the α fold proposed by Bamford, Hanby and Happey (1951) can explain these changes.

(4) It is suggested that keratin fibres are made up of micelles made up of high molecular weight protein which are set in a low molecular weight cement which is three dimensionally crosslinked by disulphide bonds.

REFERENCES

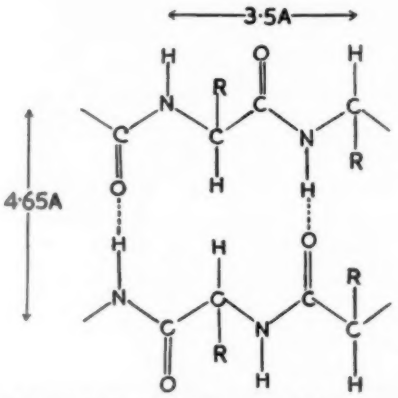
Alexander, P. (1951) Symposium on the growth, replacement and types of hair, *Ann. New York Acad. Sci.*, **53**, 24.
——, and Earland, C. (1950*a*) *Textile Res. J.*, **20**, 298.
——, ——, and Happey, F. (1950) *Nature*, **166**, 396.
——, Fox, M., and Hudson, R. F. (1951) *Biochem. J.*, **48**, 435.
——, Hudson, R. F., and Fox, M. (1950) *Biochem. J.*, **46**, 27.
Ambrose, E. J., and Elliott, A. (1951) *Proc. Roy. Soc.*, **205A**, 47.
——, and Hanby, W. B. (1949) *Nature*, **163**, 859.
Astbury, W. T., and Woods, M. J. (1933) *Philos. Trans.*, **232A**, 333.
—— (1940) *Trans. Faraday Soc.*, **36**, 871.
Bailey, J. L. (1950) *J. chem. Soc.*, 3461.
Bamford, C. H., Hanby, W. B., and Happey, F. (1951) *Proc. Roy. Soc.*, **205A**, 30.
Elöd, E., and Zahn, H. (1947) Summarized *Melliand Textilber.*, **28**, 217, 253, 291.
——, —— (1949) *Textil-Praxis*, p. 27.
Sanger, F. (1950) Summarized *Cold Spr. Harb. Symp. Quant. Biol.*, **14**, 153.
Speakman, J. B. (1947) *J. Text. Inst.*, **38**, T102.
Toennies, G., and Homiller, R. P. (1942) *J. Amer. Chem. Soc.*, **64**, 3054.
Zahn, H. (1947) *Naturforsch.*, **22**, 104.
——, and Haselmann, H. (1950) *Melliand Textilber.*, **31**, 225.

Molecular Configuration and Physical Properties of Polypeptides and Proteins

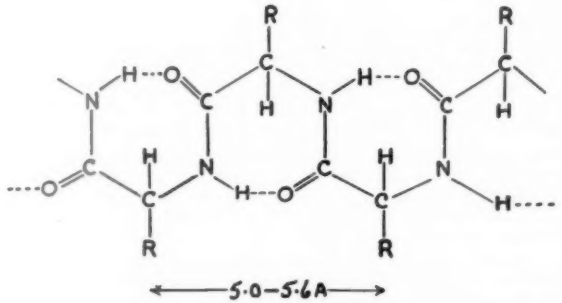
By C. H. BAMFORD, M.A., Ph.D.
Courtaulds Limited, Research Laboratory, Maidenhead, Berkshire

THE work which I am going to describe is mainly concerned with the configurations of the polypeptide chains in proteins—a theme which appears to run through all the complex variations of protein behaviour. There is no doubt that the chains in some proteins are folded; for example the globular proteins have approximately spherical molecules, and must contain chains with extensive folds. Under suitable conditions the chains may be "unwound", with the formation of thread-like molecules; the protein then loses its specificity, and belongs to the "fibrous" class.

The difficulties encountered in attempts to elucidate the nature of the folds by direct studies on proteins are formidable and are unlikely to be overcome until we have more



STRUCTURE I.—The fully extended form of polypeptide chains. Two anti-parallel chains linked by hydrogen bonds (- - - -) are shown.



STRUCTURE II.—The α_{II} fold.

knowledge of the details of the structures of the proteins. It seemed likely that some information about the ways in which polypeptide chains can fold could be obtained from an investigation of synthetic polypeptides, particularly those of high molecular weight. These substances have the same chemical backbone constitution (Structure I) as the chains in proteins, but the side chains (R) may be as simple as we please. Investigations of this kind, which have been in progress in our laboratories for the past two years, cannot be expected to provide a final answer to the protein problems, but they can help by producing useful hints.

The initial observations were made with polarized infra-red radiation. The special value of this technique is that it permits the determination of the directions in space of certain chemical bonds in molecules which have some preferred orientation, e.g. those in a stretched polymer film, or a crystal. The absorption bands of particular interest for the present purposes are those associated with the NH and CO stretching vibrations and the NH deformation vibration. These are situated at about 3,300 cm.$^{-1}$, 1,650 cm.$^{-1}$ and 1,550 cm.$^{-1}$ respectively. Absorption is strongest when the electric vector of the incident radiation is parallel to the bond direction for the stretching modes and when it is perpendicular for the deformation mode.

This technique when applied to oriented films of poly-γ-methyl-L-glutamate cast from m-cresol solution (I, R = $-CH_2CH_2COOMe$) (Ambrose and Hanby, 1949) showed that both the NH and CO bonds tend to be parallel to the main chain. This is shown by the results in Fig. 1: the NH and CO stretching modes show "parallel dichroism", i.e. absorption is strongest when the electric vector is parallel to the chain, while the NH deformation shows perpendicular dichroism. Similar results also shown in Fig. 1 were subsequently obtained for films of a number of other polypeptides cast from m-cresol or chloroform solution (Ambrose and Elliott, 1951*a*). These results indicate that these polypeptide molecules do not have the fully extended form shown in I, for in this case the NH and CO directions would be perpendicular to the chain axis. Ambrose and Hanby suggested that the chains are folded as in II; this is the simplest, but not the only, form of fold which is consistent with the infra-red observations. In it the polypeptide chain is bent to form a series of seven-membered rings, each of which is completed by a hydrogen bond. The rings and the side chains are nearly coplanar, so that the whole forms a ribbon-like structure. The NH and CO directions make angles of about 30 degrees with the main chain, in general agreement with the infra-red results. The identity period for this fold is 5·0 to 5·6A, depending on the length of the hydrogen bond, and there are two amino-acid residues in the repeat. We therefore refer to this as the α_{II} fold.

Fig. 2 shows an X-ray photograph of an oriented film of poly-γ-methyl-L-glutamate prepared from m-cresol solution. This is not the diagram which would be expected for a polymer consisting of extended polypeptide chains; the work of Astbury and his collaborators (e.g. Astbury and Street, 1931) shows that this would give reflections at 4·65A (equatorial) and 3·3 to 3·5A (polar) (*see* Fig. 5). Neither of these is present. Fig. 2 is consistent with a fibre repeat of about 5·5A, which agrees well with the α_{II} structure. Most of the reflections can be indexed in terms of an orthorhombic unit cell of dimensions a = 10·3A, b = 5·50A (fibre axis), c = 5·98A. The absence of a polar reflection at 5·5A should be noted. This would be expected if the molecule had the α_{II} structure, since the fibre axis is a twofold screw axis of symmetry. There are indications of the expected reflection at 2·75A, but the crystallinity is not sufficiently high to justify a definite conclusion. Similar results have been obtained with other polypeptides; the fibre repeats lie between 5·2 to 5·4A (Bamford, Hanby and Happey, 1951*a*, *b*).

These folded polypeptide chains bring to mind the fibrous α-proteins of Astbury's keratin–myosin–epidermin–fibrinogen group, and in fact X-ray and infra-red observations on the two classes of compound show marked similarities. The same type of dichroism is observed in a number of α-proteins (e.g. keratin, myosin) and in the folded polypeptides (Ambrose, Elliott and Temple, 1949). The X-ray photographs of two copolymers are given in Fig. 3, and are superficially similar to that of unstretched wool (Fig. 4).

Fibres of the α_{II} polypeptides show a further resemblance to those of α-proteins in that under suitable conditions they produce on stretching the β-modification, which consists of fully extended polypeptide chains as shown in I (Bamford, Hanby and Happey, 1949, 1951*a*). Fig. 6 is an X-ray photograph of a fibre of a 1 : 1 copolymer of DL-β-phenylalanine and L-leucine, after stretching 116%. Equatorial reflections at 4·65A, corresponding to the β phase, are clearly visible (*see* I), while the meridional arc shows that some unchanged α_{II} phase is present. Fig. 5 is an X-ray photograph of β-keratin for comparison. A more convenient and fairly general way of preparing the β modification is to treat the α_{II} with anhydrous formic acid. It is interesting that formic acid is also able to convert a number of α proteins to β, e.g. keratin, insulin, epidermin. Infra-red observations have confirmed that the new modification is the β form. The dichroic effects shown by the CO and NH bands are those to be expected for fully extended chains (*see* Fig. 1). It is convenient to notice here one feature of the infra-red spectrum which is very useful in practice. The actual positions of the absorption bands—particularly the CO stretching mode—are often slightly different in the α_{II} and β forms. This is clear from Fig. 1. Thus it is possible to distinguish between the two without having to resort to polarized radiation, which necessitates the use of oriented specimens. A similar frequency shift is obtained with some proteins e.g. silk, which is discussed later.

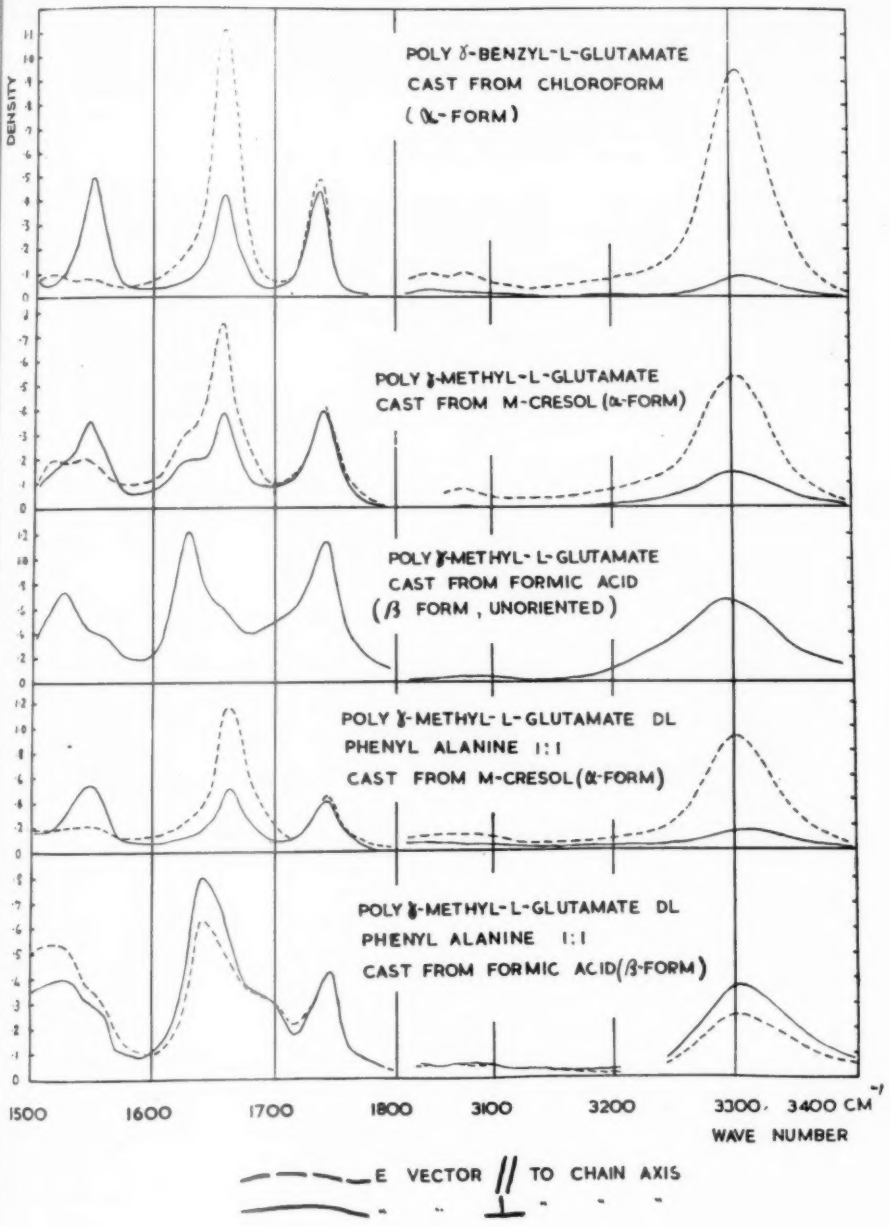


FIG. 1.—The infra-red absorption spectra of some α_{II} and β polypeptides.

The $\alpha_{II} \rightarrow \beta$ change is completely reversible; the β form is converted into the α_{II} by the action of most hydrogen bonding solvents other than formic acid, or in some cases by heating (*see* Bamford, Hanby and Happey, 1951*a*, *b*).

When the α_{II} and β forms of a number of polypeptides became available it was of interest to see how far any differences in their physical properties could be correlated with the proposed structures. One major difference between the α_{II} and β structures is in the disposition of the hydrogen bonds. In the former they are all satisfied within each chain, while in the latter they link together neighbouring chains (compare structures I and II). This produces a striking difference in solubility (Bamford, Hanby and Happey, 1950, 1951*b*). Some of the

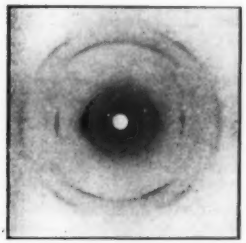


FIG. 2.

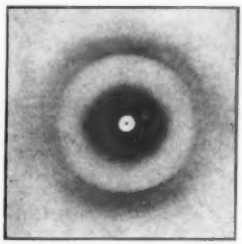


FIG. 3A.

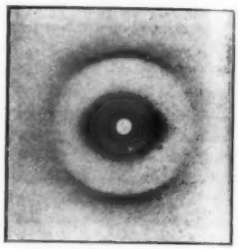


FIG. 3B.

FIG. 2.—X-ray diffraction photograph of oriented film of poly-γ-methyl-L-glutamate, prepared from m-cresol solution. Axis of orientation vertical. Cu K_α radiation; D = 4 cm.

FIG. 3.—X-ray diffraction photographs of oriented α_{II} fibres of copolymers. Axis of orientation vertical in each case. Cu K_α radiation; D = 4 cm. (A) DL-β-phenylalanine + γ-methyl-L-glutamate. (B) DL-β-phenylalanine + L-leucine.

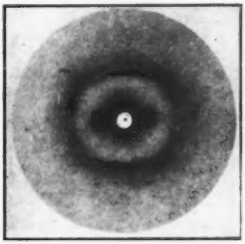


FIG. 4.

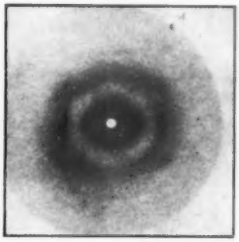


FIG. 5.

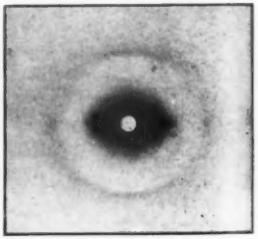


FIG. 6.

FIG. 4.—X-ray diffraction photograph of unstretched (α) wool (after Astbury).

FIG. 5.—X-ray diffraction photograph of stretched (β) wool (after Astbury).

FIG. 6.—X-ray diffraction photograph of fibre of copolymer of DL-β-phenylalanine + L-leucine after stretching 116%. Fibre axis vertical. Cu K_α radiation; D = 4 cm.

α_{II} polymers—those containing certain hydrocarbon side chains—are soluble in non-polar liquids. An example is the 1 : 1 copolymer of DL-β-phenylalanine and DL leucine, which readily dissolves in benzene or carbon tetrachloride. In these cases the β form is quite insoluble. This modification behaves in fact as a cross-linked polymer, which swells but does not dissolve; the cross links are clearly the hydrogen bonds. Moreover it has been shown that a comparatively small amount of the β form in a polymer which is mainly α_{II} is sufficient to produce insolubility in liquids which do not break hydrogen bonds. This result seems to provide evidence that in the soluble form all the hydrogen bonds must be intra-chain in character. It is important to notice that there is also direct infra-red evidence leading to the same conclusion (Ambrose and Elliott, 1951*a*).

A remarkable analogy to this has recently appeared in the protein field. It has been shown that water-soluble silk, prepared by von Weimarn's method using lithium bromide (von Weimarn, 1926), consists of undegraded fibroin in the α configuration (Ambrose, Bamford, Elliott and Hanby, 1951). The absorption spectrum is shown in Fig. 7. The CO stretching frequency is at 1,660 cm.$^{-1}$, strongly suggesting an α configuration. On stretching these

films, or treating them with alcohol or formic acid they become insoluble in water, and a new CO peak at 1,630 cm.$^{-1}$ appears. This indicates the formation of a β phase; a CO band in this position is characteristic of ordinary β silk (*see* Fig. 7). The transformation produced by these processes is by no means complete and again a small amount of β is sufficient to produce insolubility.

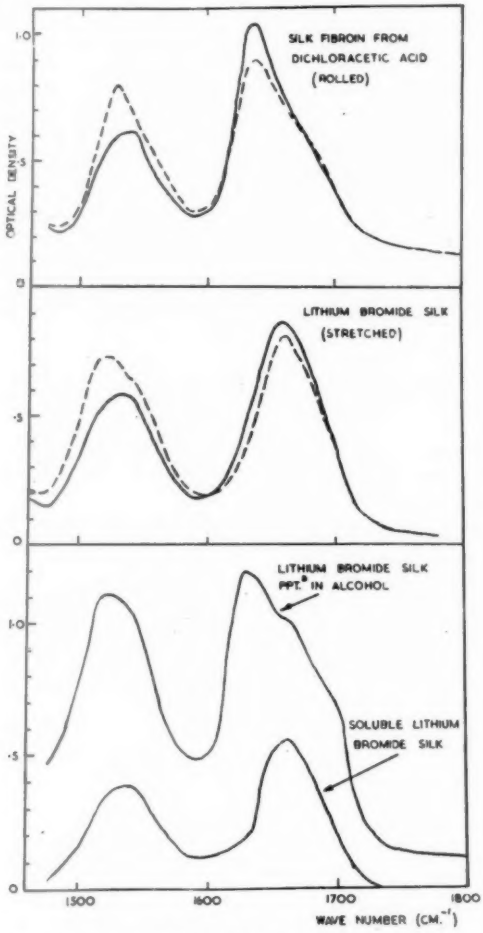


FIG. 7.—Infra-red absorption spectra of α and β silk.

A considerable amount of evidence has been collected which seems to show that the folded form of the synthetic polypeptides has the configuration II. The important question which now arises is whether this fold also occurs in proteins. This cannot be answered definitely in the absence of a complete structure determination; however the resemblances between polypeptides and proteins are often so marked that it seems likely that the α_{II} fold occurs in both. It has been suggested that the presence of the 5·15A polar arc in the X-ray photograph of porcupine quill and other fibrous α-proteins of the k-m-e-f group shows that the fold in these proteins is not the α_{II}. This argument does not seem conclusive; there are several possible explanations of the presence of such an arc which are compatible with the α_{II} structure. Moreover there is at least one example of a fibrous protein which does not show this polar arc—the muscle protein studied by Lotmar and Picken (1942). This substance gives an X-ray photograph which is remarkably similar to that of Fig. 2.

If there is a single α fold of general occurrence in proteins (and this is at present only conjecture) it will probably possess the following properties in addition to agreeing with the X-ray and infra-red evidence: (*a*) all the hydrogen bonds will be intrachain in character, (*b*) the folded form will be flexible, to allow for phenomena such as muscular contraction, and (*c*) there should be no large or awkward relative movements of side chains in the transformation $\alpha \rightarrow \beta$, since this may be readily effected, and does not involve the rupture of cystine cross links when these are present, e.g. in keratin, or insulin. We believe that the α_{II} fold is the only one which satisfies these conditions, and we therefore regard it as the basic primary fold in proteins. Recent work has shown that a number of globular proteins have the α configuration (Ambrose and Elliott, 1951*b*); the spherical shape of the molecules shows, however, that extensive secondary folding of the chains, over and above the primary fold, must occur. The α_{II} fold, as Dr. Conmar Robinson has pointed out, is not only capable of secondary folding, but seems to be the only one that allows compact secondary folding in a plane to which the side chains are normal, without breaking of hydrogen bonds. This arrangement may account for some aspects of specificity. The primary fold is probably not specific.

The difference in the solubilities of the α and β forms of proteins might have important biological implications, since it is possible that the $\alpha \rightarrow \beta$ change may be brought about by comparatively small changes in the nature of the environment.

The relative stabilities of the α and β forms of a protein are probably dependent *inter alia* on the size of the side chains, small side chains favouring the β form (as e.g. in silk). Thus short sections of a protein chain containing a preponderance of short side chains might make the molecules particularly ready to assume a partly β and insoluble form. This in our view is the kind of process that Nature uses in fibre formation by silkworms and spiders, and the possibility that she has used it for other purposes provides an attractive field for speculation and experiment.

REFERENCES

AMBROSE, E. J., BAMFORD, C. H., ELLIOTT, A., and HANBY, W. E. (1951) *Nature*, **167**, 264.
——, and ELLIOTT, A. (1951*a*) *Proc. Roy. Soc.*, **205A**, 47.
——, —— (1951*b*) *Proc. Roy. Soc. B.* In course of publication.
——, ——, and TEMPLE, R. B. (1949) *Nature*, **163**, 859.
——, and HANBY, W. E. (1949) *Nature*, **163**, 483.
ASTBURY, W. T., and STREET, A. (1931) *Philos. Trans.*, **230**, 75.
BAMFORD, C. H., HANBY, W. E., and HAPPEY, F. (1949) *Nature*, **164**, 751.
——, ——, —— (1950) *Nature*, **166**, 829.
——, ——, —— (1951*a*) *Proc. Roy. Soc.*, **205A**, 30.
——, ——, —— (1951*b*) *Proc. Roy. Soc. A.* In course of publication.
LOTMAR, W., and PICKEN, L. E. R. (1942) *Helv. Chim. Acta*, **25**, 538.
VON WEIMARN, P. P. (1926) *Canad. Chem. & Met.*, **10**, 227.

Section of Obstetrics and Gynæcology

President—V. B. GREEN-ARMYTAGE, F.R.C.O.G., M.D., F.R.C.P.

[*November* 17, 1950]

DISCUSSION ON SYMMETRICAL CORTICAL NECROSIS OF THE KIDNEYS

Professor H. L. Sheehan[1]: Renal cortical necrosis is a common sequel to concealed accidental hæmorrhage. The examination of the kidneys of a series of women who died at various times following accidental hæmorrhage shows all the stages of the development of cortical necrosis and also of a series of other ischæmic lesions less severe than cortical necrosis. All the lesions are due to a spasm in the arterial tree of the cortex, varying in its site and in its duration. When the spasm passes off, blood flows again into the damaged tissue. If the glomeruli are dead, this leads to thrombosis or stasis in them. If arteries are dead, thrombosis occurs in their lumen.

The lesions which occur can be arranged in nine groups: simple albuminuria, colloid degeneration of tubules, necrosis of proximal tubules, benign thrombosis of glomeruli, and focal, minor, patchy, or gross renal cortical necrosis, the latter being of two types. The clinical differentiation of all but the most trivial of these lesions can be rather difficult in the early puerperium. The two most useful guides are the output of urine and the concentrating power of the kidney. Hæmaturia is indicative of glomerular damage but does not indicate the extent of the lesions. The blood chemistry during the first week is not a good guide to the pathological state of the kidneys.

Dr. A. M. Joekes[1]: In a study with Dr. G. M. Bull and Dr. K. G. Lowe of some 120 cases of anuria or low specific gravity oliguria a group of 10 cases fall into the possible diagnosis of cortical necrosis. Of these 5 were fatal cases; 4 cases showed the classical picture of bilateral symmetrical cortical necrosis, and of these 3 were associated with pregnancy and concealed accidental hæmorrhage; the fourth case with the typical lesion was in a man, with an obscure ætiology but possibly associated with sepsis. The fifth fatal case showed a patchy cortical necrosis but with tubular damage in nephrons in which the glomeruli were normal and occurred in a pregnant woman presenting with a clinical picture similar to the other 3 fatal cases, i.e. with concealed accidental hæmorrhage preceded by evidence of toxæmia. The remaining 5 cases falling into this group were all pregnant women presenting with ante-partum hæmorrhage; in some cases there was revealed hæmorrhage, but in all there was placental infarction and retro-placental clot. 3 of these cases had anuria or low specific gravity oliguria lasting six or more days, the other 3 had anuria lasting only twenty-four to forty-eight hours. Functional studies showed the renal damage in the surviving cases to run a course identical with acute tubular necrosis, with eventual almost complete recovery of renal function.

It is argued that cortical necrosis is the irreversible end-point of very severe renal ischæmia, and that in cases of "incomplete cortical necrosis" in which recovery is possible, the renal lesion is acute tubular necrosis, the ischæmia not having been severe enough to lead to the necrosis of the bulk of entire nephrons. In such cases patches of irreversible necrosis, possibly only affecting single nephrons, may occur.

Professor K. J. Franklin,[1] approaching the problem as a physiologist, said that experimentally renal cortical necrosis can be produced by ischæmia, and that it is probably never *un*associated with ischæmia. It has been produced by continuous or intermittent interruption of the whole renal circulation for periods of time varying with the genera of animals used, and has then been accompanied by less severe changes in the more resistant medulla. It has also been caused by intermittent faradic stimulation of the renal nerves for a few hours, with a subsequent period of rest; an interesting feature is that some degree of recovery can on occasion occur during the rest period, suggesting that some human cases may be undiagnosed on account of a similar return towards normal. Finally, it has resulted from administration of various chemical substances. In the last two types of experiment there has been seen diversion of the renal cortical blood flow,[2] and it is not impossible that such diversion, with its infinite variety in extent and in duration, is a factor common both to cortical necrosis and to other renal troubles of human pregnancy. Such diversion has been produced experimentally not only in the rabbit, but also in the monkey, dog, cat, rat, mouse, guinea-pig, and (Amoroso, 1950) seal, i.e. in all the mammals so far tested, so it is not improbable in man.[3]

[1] Greatly abridged.

[2] *See* Trueta *et al.*, 1947; Franklin, 1950.

[3] Since the Sectional Meeting, a beginning has been made in the obtaining of more direct evidence on this point.

Chemical substances circulating in the blood stream can in some instances act upon nervous centres and thereby affect the renal circulation *via* the renal nerves.[1] In other instances they produce their effects in animals which have been adrenalectomized and have had their renal nerves divided. In such cases there are two possibilities, a direct action upon the intrarenal vascular system or an action upon that system *via* an intrarenal nervous apparatus.

Recent studies upon the renal innervation (Mitchell, 1950; Knoche, 1950; De Muylder, 1950; Asfoury, 1950), while on the whole lending support to the possibility of the second alternative, are by no means in agreement as to details, and in any case the final proof of any intermediation of an intrarenal nervous mechanism must come from experimental work. As preventive and therapeutic procedures (apart from extrarenal denervation or nerve-blocking where such is indicated) depend upon a decision between the two alternatives mentioned, such further research is urgently required.

Professor Franklin ended by referring to an experiment, carried out by Dr. A. M. Miles and himself, in which a doe gave birth spontaneously, and both humoral and nervous influences caused diversion of the renal cortical blood flow. It seemed likely that the posterior part of the pituitary gland was the source of the humoral influence, while a uterorenal reflex was the nervous one.

He left it to the Section to assess how far the experimental findings mentioned by him were applicable to explanations of the renal complications of human pregnancy.

REFERENCES

Amoroso, E. C. (1950) Unpublished observation.

Asfoury, Z. M. El (1950) Demonstration to the Fifth International Anatomical Congress, Oxford.

De Muylder, C. (1950) Tissue nerveux et pathologie rénale. Paris.

Franklin, K. J. (1950) *Proc. R. Soc. Med.*, **43**, 467.

Knoche, H. (1950) *Z. Anat. EntwGesch.*, **115**, 97.

Mitchell, G. A. G. (1950) *Acta anatom.*, **10**, 1.

Trueta, J., Barclay, A. E., Franklin, K. J., Daniel, P. M., and Prichard, M. M. L. (1947) Studies of the Renal Circulation. Oxford.

Dr. J. F. Heggie: In the papers presented, Professor Sheehan has outlined most clearly the morbid anatomical and histological changes in the kidney consequent upon ischæmia of varying duration and thereby illustrated one of the fundamental principles of pathology—that interruption of the blood supply to an organ or structure is followed by degrees of damage which range from the most minor, attended by temporary functional derangement from which full recovery is possible, to the more severe that produce partial structural damage, and finally to the most severe which result in necrosis or death of the part. He attributed the ischæmia to arteriolar and arterial spasm but left undefined the cause of the spasm.

In describing the altered (diminished) renal function measured in cases surviving incomplete renal cortical necrosis, and, in indicating that the changes in renal function and the mode of recovery are identical with those seen in tubular necrosis, Dr. Joekes too has illustrated the fundamental principle already mentioned and his conclusions can be said to be based upon it.

In the initial stages of experimental renal cortical necrosis I have observed that oliguria is associated with the passing of urine whose composition is practically identical with glomerular filtrate, thus indicating fairly complete loss of tubule function at that early stage. Also in the rabbit, Badenoch and Darmady (1947) showed that renal tubule cells can regenerate after ischæmia lasting up to one hour and it was suggested that, as the corresponding time interval in the dog is longer, in man ischæmia for up to six hours would be unlikely to result in permanent renal damage.

Professor Franklin has indicated the several ways in which renal ischæmia can be brought about and in which there is a *diversion* of the main cortical blood flow. [It is well that Professor Franklin now employs the term *diversion* and has renounced the term "Oxford shunt" (1949, 1950). I have all along advocated the use of the more accurate word *diversion* for this occurrence. It is the correct term as there is no anatomical vascular shunt in the kidney (1946; 1949, *a*, *b*).] The local nervous reflex mechanism described in the kidney is probably responsible for the alteration of renal blood flow, when, in man, there is a 50% reduction on assuming the upright from the recumbent posture. In the normal rat Byrom and Dodson (1948) induced and observed transient spasm of renal arterioles following sudden increase of intra-arterial tension from the intra-arterial injection of warm Ringer's solution. In pregnancy toxæmia, in which there is increased arterial tension, it is possible that the nervous mechanism responsible for the local control of the intrarenal blood flow is unduly "irritable". In response to concealed accidental hæmorrhage this mechanism may over-act for over-long and after prolonged ischæmia symmetrical renal cortical necrosis results.

[1]This paragraph is based partly on personal findings and partly on those of other workers in the Department of Physiology of St. Bartholomew's Hospital Medical College; the studies of Dr. J. E. Cotes deserve special mention in this connexion.

REFERENCES
BADENOCH, A. W., and DARMADY, E. M. (1947) *J. Path. Bact.*, **59**, 79.
BYROM, F. B., and DODSON, L. F. (1948) *J. Path. Bact.*, **60**, 357.
FRANKLIN, K. J. (1949) *Proc. R. Soc. Med.*, **42**, 380.
—— (1950) *Proc. R. Soc. Med.*, **43**, 471 (footnote).
HEGGIE, J. F. (1946) *Lancet* (ii), 436.
—— (1949) (*a*) *Brit. Med. J.* (i), 151; (*b*) *Proc. R. Soc. Med.*, **42**, 380.

Mr. J. Sophian: Professor Sheehan has shown that arterial spasm is the basis of the renal breakdown associated with concealed accidental hæmorrhage, while Professor Franklin has noted the pattern of the renal cortical blood flow diversion produced in various ways in the experimental animal, leaving it to be decided if this pattern is followed in our obstetrical cases and, if so, whether it is humorally or nervously intermediated.

For my part, I shall attempt the decision in respect both of cortical necrosis and of its precursor, pre-eclamptic toxæmia. The latter, in its prodromal oliguric stage, offers exceptional opportunities for the study of renal function during the development of suppression; Homer Smith (in a lecture statement, 1950) said that only twice, outside pregnancy, has it been possible to make such a study, and that in both instances evidence of glomerular shut-down was revealed. Is it so also in the toxæmias of pregnancy as a prelude to renal failure?

Firstly, an appreciably depressed inulin filtration rate indicating glomerular shut-down which returns to normal shortly after delivery has been shown to occur in pre-eclamptic toxæmia by Corcoran and Page (1941), by Dill *et al.* (1942), by Taylor *et al.* (1942), by Odell (1947), and most recently by Kenney, Lawrence and Miller (1950) at Leeds. In view of the rapidity of the post-partum recovery, organic change in the glomerulus appears to be excluded, leaving spasm of the afferent arteriole as the remaining explanation which must, I think, be accepted.[1]

Scriver and Oërtel (1930) held that the initial disturbance *is* vasomotor and dependent on "irritations of the arterial terminal segments of different intensities". They went on to note that the most severe stimulation of the arteries had as a sequel *vaso paralysis*, with consequent stasis and thrombosis.

Ash (1933) also thought that an angioneurotic disturbance *was* an initiating factor. Shaw Dunn and Montgomery (1941), who actually quoted these views, propounded a different view of the ætiology, despite the fact that they described survival of the subcapsular and juxtamedullary regions, that is to say, an intracortical distribution of necrosis, which avoided these areas. They should have realized from seeing such a pattern that a nephrotoxin acting directly on the cells was not in question, but that nerve stimulation might very well so be. Trueta and his colleagues, a few years later, published this more rational explanation, with its selective distribution of vascular effects.

Indeed it was this which suggested to me the hypothesis which I have been advancing since 1947, about the causation of the major renal disturbances that underlie pregnancy toxæmia.

On the experimental side, shunting the kidney in the laboratory animal by intermittent faradic stimulation of the renal nerves can result in visible changes in the cortex such as cellular œdema and in one instance some degree of cortical necrosis. These are outcomes of the experiments to which Professor Franklin alluded. [Photomicrographs were then shown.] In each experiment the opposite kidney served as a control; the pathological diagnoses were made in the first instance by Dr. G. J. Cunningham and thereafter by Professor J. H. Dible, to both of whom we express our acknowledgments.

An interesting further finding in one of these experiments was that, during a recovery period following the stimulation, the area damaged by the ischæmia lessened in extent (Franklin, 1950); this was what prompted Professor Franklin's suggestion (*see above*) that it may be possible for cases of human cortical necrosis to clear up without ever having been diagnosed as such.

A third point was that a humoral substance passed with the circulation from the stimulated kidney during the recovery period, and caused paling of the unstimulated control kidney. I believe that this observation explains the reduced filtration rate which occurs in mammals for some time after removal of the clamps which have been applied to the renal arteries in order that the effects of total arrest of the circulation may be studied. Ever since Richards (1929) showed in the *frog* that such procedure led to complete tubular reabsorption of the glomerular filtrate, it has been widely assumed that this is the explanation of the renal failure in *human subjects* which we are reviewing this evening. For my part, however, I consider that afferent arteriolar spasm, with consequent decrease or cessation of the glomerular blood flow, is the ætiological basis, that the initiation of the spasm is provoked as I suggested (1949) to this Section, and that its continuation results from liberation of a pressor substance from the ischæmic kidney during its recovery. Successful outcomes of exsanguination transfusion procedures in the treatment of post-abortion anuria have been

[1] Incidentally, Corcoran and Page found they could offer no explanation of the renal functional pattern in crush syndrome and related stages other than a diversion of the renal cortical blood flow such as was first described by Trueta *et al.* (1947).

reported by Vallery-Radot *et al.* (1950). The efficacy of this measure is in line with the thesis which I advance, and so is the marked rise in blood pressure in the early stages of recovery from anuria.

Finally, there is the evidence from other lines of treatment. Great credit is rightly accorded to Drs. Bull, Joekes and Lowe for the measures they have formulated, especially to combat the mounting water and sodium retention in the acute renal failure stage. But if we accept the view that glomerular arteriolar spasm underlies the mechanism of anuria, then it is evident that the longer the spasm obtains the greater will be the damage to the tubules, which are dependent for their blood supply mainly upon the glomerular efferents. The greater, too, will be the production of renal pressor substance resulting from the cortical ischæmia, and this substance will in its turn tend to aggravate the spasm. Recovery would result from the abatement of the stimulus or from inability for further response on the part of the vaso-constrictor apparatus, through therapeutic measures interrupting conduction along the renal nervous arcs. Such measures include Hingson's technique of caudal analgesia in which the fall of blood pressure is prevented by pavex action. From the times taken for successful results with this treatment inferences may be drawn as to the rate of recovery of the damaged tubular cells *vis-à-vis* the period of ischæmia they have sustained. I cannot agree with Homer Smith that there is a time limit for the initiation of the treatment, for Hingson has achieved excellent results at all periods of the anuric state; though the advantages of early commencement of this therapeutic procedure are obvious.

I believe that this success is due to the fact that accompanying the gross histological changes Professor Sheehan has demonstrated there is continuous though incomplete spasm of the remaining nephronic vasculature. The afferent arteriolar spasm reduces the head of pressure in these glomerular capillaries below the effective osmotic pressure of the blood it contains and results in the observed anuria. It is this spasm that Hingson relieves and by such procedure dramatically swings the balance in favour of renal recovery proven by the early onset of diuresis of glomerular filtrate.

REFERENCES

Ash, J. E. (1933) *Amer. J. Med. Sci.*, **185**, 71.
Corcoran, A. C., and Page, I. H. (1941) *Amer. J. Med. Sci. New Ser.*, **201**, 385.
Dill, L. V., *et al.* (1942) *Amer. J. Obstet. Gynec.*, **43**, 32.
Franklin, K. J. (1950) *Proc. R. Soc. Med.*, **43**, 467.
Hingson, R. A. (1949) *Brit. med. J.* (ii), 777.
Kenney, R. A., Lawrence, R. F., and Miller, D. H. (1950) *J. Obstet. Gynæc.*, **57**, 17.
Odell, L. D. (1947) *Amer. J. med. Sci.*, **213**, 709.
Richards, A. N. (1929) *Trans. Ass. Amer. Phys.*, **44**, 64.
Scriver, W. de M., and Oërtel, H. (1930) *J. Path. Bact.*, **33**, 1071.
Shaw Dunn, J., and Montgomery, G. L. (1941) *J. Path. Bact.*, **52**, 1–16.
Sophian, G. J. (1949) *Proc. R. Soc. Med.*, **42**, 387.
Taylor, H. J., Jnr., Wellen, I., and Welsh, C. A. (1942) *Amer. J. Obstet. Gynec.*, **43**, 567.
Trueta, J., *et al.* (1947) Studies of the Renal Circulation. Oxford.
Vallery-Radot, M., *et al.* (1950) *Bull. Soc. med. Hôp. Paris*, **66**, 454.

Mr. R. H. Paramore [*Abridged*]: Of the three main explanations of this necrosis—that it is caused by (*a*) a toxin; (*b*) reflex nervous stimuli; (*c*) excessive activity of the abdominal wall muscles—the first two are untenable for the inner part of the cortex remains unaffected. They both posit that the anuria is a consequence of a preceding cellular disturbance: but since the juxta-medullary cortex persisted intact, was it not odd that it also did not produce urine? The third explanation, held in some esteem a century ago but now in disfavour, was different. According to it, the anuria occurs first and causes the necrosis. The common occurrence of this necrosis in concealed accidental hæmorrhage is clinical evidence.

In the early sequence of this change, Malpighian corpuscles, even those situated in the outer two-thirds of the cortex, are active; and the convoluted tubules everywhere are distended with urine. If a toxin or a vaso-constriction were the cause, they should be empty of urine. The biopsies shown by Clifford White in 1919, and his slide exhibited at the January 1949 meeting, demonstrated these phenomena. I have sections—from a case of anuria and from one of fulminant eclampsia—showing similar changes. Bowman's capsules in the outer part of the cortex contained fluid, evidence of activity of the Malpighian corpuscles: and the convoluted tubules were fully distended. They were also distended in the juxta-medullary cortex. The same features were to be seen in a microscopic slide from a case of crush-syndrome, shown by Professor J. H. Dible in May (1950, *Brit. med. J.* (i), 1262). In my own slides, the cells lining the convoluted tubules were all flattened; and their nuclei appeared intact. The picture presented was one of intrarenal–intracortical retention of urine. It is this which causes the necrosis in the outer part of the cortex. The juxta-medullary part remains intact because blood is still thrust through it: but the urine produced cannot escape.

REFERENCE

White, Clifford (1919) *Proc. R. Soc. Med.*, **12**, Obstet. and Gynæc., 29.

Dr. Z. M. El. Asfoury summarized his work to which Professor Franklin had referred: The kidney has a rich nerve supply which it receives by two routes. Many nerve trunks run along the renal arteries, while other nerve fibres reach the kidney by way of the capsule. These two different routes may have some bearing on the problem of renal cortical necrosis which is being discussed to-night.

It has been established that the renal blood vessels go into spasm under different conditions such as when the animal is deprived of oxygen. The kidney responds by contracting to a smaller size, the capsule may wrinkle and the cortex may become pale or mottled with white patches like the kidney with cortical necrosis. These manifestations can also result from stimulating the renal nerves. Normally impulses arise from higher centres in the central nervous system, which influence the kidney functions and its blood circulation. Such impulses can be interrupted by severing the connexions to the kidney.

After left thoraco-lumbar sympathectomy or peri-arterial strip and capsulectomy in rats and after varying periods of degeneration the two kidneys were exposed. Some of them showed striking appearance. On opening the abdomen, under anæsthesia, it was noticed that the left kidney and its blood vessels were much larger than the right kidney and its vessels. This probably occurred as a result of the stimuli arising from opening the abdomen reflexly affecting the rat kidney. On obstructing the trachea to deprive the animal of oxygen, the denervated kidney remained unaffected while the normal one contracted even more in size, its capsule wrinkled and its cortex became mottled.

These denervated kidneys, which gave this physiological test of nerve degeneration, were examined microscopically. Many nerve fibres had disappeared but numerous intact ones with their mother nerve cells were seen at different sites inside the renal tissue. This supported my previous findings of nerve cells inside the kidney together with synaptic formations. These ganglionic formations became much simpler after degeneration. I believe that these rich intrinsic nerve fibres and nerve cells are the sites for local reflexes which take place inside the kidney, under the influence of higher centres or when they become independent from them.

Professor Sheehan has pointed out that certain areas of the cortex which are around the hilum of the kidney show complete early necrosis while the rest of the cortex shows only patchy lesions in the early stages at least. I believe this may be due to the peculiar vascular and nerve supplies of the kidney and their distribution. As I said before, the nerve trunks lie in relation with the main arteries of the kidney. The nerve trunks follow the arterial branches throughout their course. The calibre of the renal arteries decreases gradually and so does the size of the nerve trunk and the number of contained fibres.

As their arteries arise directly from the main renal arteries the areas of the cortex round the hilum receive a rich vascular supply and accordingly a rich nerve supply. The other parts of the cortex are supplied by the terminations of much smaller end-branches of the renal artery after crossing the depths of the medulla. In fact these lesions in the cortex around the hilum appear to me to support the interpretation that cortical necrosis is due to vascular spasm of nervous origin. If the cause is a toxin, one would think that all the renal tissue ought to be affected equally instead of the damage being discrete and patchy.

It is for these reasons that I consider the lesions of cortical necrosis to be due to vascular spasm under nervous influence.

Professor J. Trueta: Hamilton in 1833 and Juhel-Rénoy in 1886 first called attention to this condition. They observed cases of symmetrical cortical necrosis of the kidneys during the febrile period of scarlet fever. It was not until 1898 that Rose-Bradford and Lawrence reported the first case of symmetrical cortical necrosis following abortion. Later Bramforth described a case of symmetrical cortical necrosis during the course of Weil's disease. My personal interest in this problem started at the time when Bywaters and his colleagues reported the first recent description of kidney failure during what they named "crush syndrome".

My interest in the behaviour of the kidney in shock had started some years earlier. I was acquainted with the work of Claude Bernard and with his belief that the kidneys were the organs mainly responsible for maintaining the constancy of the "milieu interieur" and it seemed logical to assume that a regulating mechanism must exist in the kidney to keep this internal medium constant. On purely theoretical grounds I assumed that the response of the kidney to any nervous stimulus was an arterial contraction, and possibly arterial spasm. The result of these repeated stimuli was the reduction of the blood flow of whole, or part, of the kidney, and it was not until some years later when working with my colleagues at the Nuffield Institute for Medical Research at Oxford, that we discovered the contrasting behaviour of the vessels of the cortex with those of the medulla and the tendency of the cortical vessels to contract when stimulated electrically, by toxins and by some hormones.

A perusal of the bibliography available reveals that a number of previous investigators had been struck by the readiness of the renal cortical arterioles to contract when compared with those of the rest of the kidney, and with the arterioles of other organs. For instance the

work of the Japanese school of Tamura (1927) revealed that hæmorrhage in the frog causes spasm of the arterioles of the renal cortex while not affecting the capillary circulation in other parts of the body. In 1934 Adolph reported the same behaviour of the renal cortical arterioles in asphyxia. Bick, Kempton and Richards (1938) found also in the frog that the renal arterioles which are connected with glomeruli constrict with oxygen lack whereas the remainder of the renal arterioles and the arterioles of all the other organs of the body dilate. This dilatation was in accordance with the work of Krogh, who in 1929 reported that oxygen lack decreased the contraction of smooth muscles, a view which has been recently confirmed in rats by Furchgott and Shorr for the muscles of the gut. K. J. Franklin (1949) has confirmed some of these observations. This tendency of the cortical arterioles to contract as a single pattern of behaviour after any stimuli might serve to explain the findings reported by Van Slyke (1946) and his collaborators in the dog's kidney during shock. They observed that in experimental hæmorrhagic shock there is an increased oxygen consumption in every organ of the body which was examined except in the kidney. They describe the intense vasoconstriction of the kidney under conditions of shock and suggest that the reduction of the renal blood flow caused by such a constriction contributes to the survival of the experimental animal, increasing the volume of blood available for the higher centres. It is interesting to note that while all the rest of the organs examined by these authors had increased their oxygen consumption during shock, the kidney had the unique behaviour of decreasing oxygen consumption under the same condition. A possible explanation of how this occurs is that only the cortical vessels contract while the medullary vessels remain permeable to the circulation of the blood, and thereby a considerable volume of tissue no longer makes its demands upon the oxygen content of the blood. In cases with very marked renal artery constriction the whole of the kidney may be ischæmic, but probably in the greater majority of cases the cessation of blood circulating in the kidney may only affect those parts of the cortex whose vessels are most sensitive to any stimuli and readily constrict. That is, those parts of the kidney not intimately connected with either the capsular blood flow which comes from the periphery of the kidney, or with the juxta-medullary system of vessels, both of which may escape the constriction and remain permeable. It seems to me illogical thinking not to admit that a mechanism which, when freely operating, may cause total necrosis, might also operate on such a reduced scale as to cause either only transient ischæmic damage to limited portions of the kidney or else may cause permanent but scattered ischæmic lesions which are not sufficient to interfere seriously with the function of the organ. Thus our conclusions support Professor Sheehan's remarks.

While only nine groups of initial ischæmia are mentioned in Sheehan's classification I would say that he could have presented a hundred, for this is a mechanism of functional disturbance causing renal damage which may go from total health to total necrosis. I assume that Professor Sheehan has arranged his cases in nine groups only for purpose of classification. It is also interesting to note in his communication how the severity of the tubular lesions are related to the length, and perhaps the intensity, of the ischæmia. The tubules, being the most highly differentiated part of the kidney, must be the earliest victims of ischæmia. Until we have a clear conception of the mechanism underlying cortical ischæmia we will not be able to find the appropriate treatment. We should direct all our attention to finding a method of preventing the vessels of the renal cortex from going into spasm—whether reflex renal cortical spasm following distension of the uterus as suggested by Mr. Sophian, or spasm due to the action of toxins, or other causes. As Dr. El Asfoury has stated, the kidney seems to be extremely rich in nervous cells and it may be that continuous caudal anæsthesia is only a partial answer to to-night's problem as it does not act on the intrarenal nervous cells.

REFERENCES

Adolph, E. F. (1934) *Amer. J. Physiol.*, **108**, 177.
Bick, L. V., Kempton, R. T., and Richards, A. N. (1938) *Amer. J. Physiol.*, **122**, 676.
Bradford, J. R., and Lawrence, T. W. P. (1898) *J. Path. Bact.*, **5**, 195.
Bramforth, J. (1923) *J. Path. Bact.*, **26**, 4045.
Franklin, K. J., McGee, L. E., and Ullmann, E. (1949) *Proc. Soc. exp. Biol. Med.*, **71**, 339.
Furchgott, R. F., Shorr, E., and Zweifach, B. W. (1948) *Ann. N.Y. Acad. Sci.*, **49**, 571.
Hamilton, G. (1833) *Edin. Med. Surg. J.*, **39**, 140.
Juhel-Rénoy, E. (1886) *Arch. Gén. Méd.*, **17**, 385.
Krogh, A. (1929) The Anatomy and Physiology of Capillaries. New Haven.
Tamura, K. (1927) *J. med. Sci.* (Pharmacol.), **1**, 211.
Van Slyke, D. D., Dole, V. P., and Phillips, R. A. (1946) *Amer. J. Physiol.*, **145**, 337.

Dr. G. M. Bull: On histological and on functional grounds there appears to have been general agreement that spasm and ischæmia cause graded lesions to complete necrosis. In practice we must seek treatment to relieve this spasm. In the onset phase denervation of the kidney would be desirable but the patient is shocked. Later denervation is futile because the blood flow through the kidney is mechanically mediated.

FIG. 1.—The patient. Note the peri-oral distribution of the melanin spots.

FIG. 2.—Photograph showing the melanin spots on the buccal mucosa.

FIG. 3.—Gastroscopic view of some of the gastric adenomata.

Clinical Section

President—W. A. BOURNE, M.D.

[*December* 8, 1950]

Gastric and Jejunal Polyposis Associated with Melanin Spots of the Oral Region and Digits.—NORMAN C. TANNER, F.R.C.S.

In 1896 Sir Jonathan Hutchinson described identical twins who had a number of pigmented spots on the lips and inside of the mouth. In 1919 Dr. F. Parkes Weber reported a follow-up of these cases, and noted that one of the twins had died of intussusception. In 1921 Peutz described a case in which several members of a family had pigment spots on the mouth, hands and feet associated with intestinal polyposis. In 1944 Foster found a father and daughter with facial pigmentation and intussusception due to polyposis, and 2 other similar cases in the same family. I know of no cases from the British Isles apart from Hutchinson's, Foster's, and this present case. In 1944, however, Jeghers reported 2 similar cases from the United States, and again in 1949 Jeghers, McKusick and Katz reported 10 cases collected from American sources. Of the 10 cases, 8 had been operated on for intussusception initiated by jejunal polyps; 1 of the 8 was reported to have had four operations for intussusception. These writers reported that by 1949 they had collected 12 cases from the world literature and added 10 from America.

From a survey of the recorded cases it is evident that the disease usually manifests itself early in life. The most notable feature of the condition is the consistent and peculiar distribution of pigmentation, mostly round the lips and adjacent buccal mucosa. The patches are round, oval or irregular, and vary from brown to almost black. Biopsy specimens (Jeghers *et al.*) show on microscopy vertical bands of melanin pigment. All of the patients are of dark complexion. Associated with the pigmentation is polyposis of the entire intestine, most consistently producing symptoms from small intestinal involvement.

Case report.—A. W., a brunette aged 17, was admitted to St. James' Hospital on 9.2.50, complaining of six weeks' epigastric discomfort shortly after meals—which was relieved by vomiting—and a general feeling of increasing weakness. Her past history revealed nothing significant. Her father, mother and two younger sisters were healthy, though it was noted that the younger sister had pigment spots round the mouth.

On examination she was seen to be pale, thin and asthenic. She had dark pigment spots mainly concentrated round the mouth, particularly on the lower lip and nose tip (Fig. 1). Other similar spots were present on the front of the neck, dorsum of the fingers, and a few on the forearm and hand, the back of the neck, dorsum of the feet, front of the shins, knees and thighs. Others were present on the red part of the lip and in the buccal cavity (Fig. 2) and on the palate.

She stated that these pigment spots had been present since the age of 5. There was some diffuse thyroid enlargement, and spinal kyphosis.

Abdominal examination revealed no gross abnormality at first. Blood count: R.B.C. 3,500,000; W.B.C. 9,700 per c.mm.; Hb 55%. Differential leucocyte count normal. Serum chloride, sodium and potassium values were within normal limits.

She was at first suspected of having Addison's disease, but persistent vomiting and pain caused her to be referred for a surgical opinion on 18.2.50. When seen on this date she had visible intestinal peristalsis in the left abdomen, and straight X-ray of the abdomen confirmed the presence of dilated loops of small bowel.

The abdomen was explored through a left paramedian incision under general anæsthesia. An intussusception involving three feet of bowel just distal to the duodeno-jejunal flexure was found, and reduced. On palpation after reduction it was evident that there were innumerable small sessile and pedunculated polypi involving the upper six feet of jejunum, and one large one which had initiated the attack. The bowel was opened and the large polyp and some eight smaller ones removed, but many seedling polypi remained in the part examined.

Following the operation the patient made a complete recovery. Histological examination disclosed that the tumours were simple adenomatous jejunal polyps showing acute on chronic inflammation.

Since recovery the following investigations have been carried out:

Barium Meal: No gastric or jejunal abnormality.

Œsophagoscopy: Normal œsophagus.

Gastroscopy: The mucosa was of normal texture. The pylorus, antrum and angulus were normal. In the body of the stomach were twelve to fifteen adenomata, probably 0·3–0·6 cm. in diameter; all but one were sessile, and none was ulcerated (Fig. 3).

Proctoscopy: No pigmentation in the anal region.

Sigmoidoscopy: No adenomata present within 12 inches of the anus.

Cystoscopy: Normal bladder.

REFERENCES

FOSTER, D. B. E. (1944) *Brit. med. J.* (ii), 78.
HUTCHINSON, J. (1896) *Arch. Surg. Lond.*, **7**, 290.
JEGHERS, H. (1944) *New Engl. J. Med.*, **231**, 88.
——, MCKUSICK, V. A., and KATZ, K. H. (1949) *New Engl. J. Med.*, **241**, 993 and 1031.
PEUTZ, J. L. A. (1921) *Ned. Maandschr. Verlosk. (Geneesk)*, **10**, 134.

Dr. F. Parkes Weber said that the only part that he had taken in regard to the interesting, but extremely rare developmental syndrome in question, was writing a paper on "Patches of deep pigmentation of the oral mucous membrane not connected with Addison's disease", 1919, *Quart. J. Med.*, **12**, 404. In this paper the twins described by Sir Jonathan Hutchinson and Dr. J. R. T. Conner were included, with information kindly supplied by Dr. Conner, who arranged for Dr. Weber to see the one who was still living. Dr. McKusick afterwards corresponded with Dr. Weber on the syndrome (*see* H. Jeghers *et al.* (1949) *New Engl. J. Med.*, **241**, 993).

Sjögren's Syndrome.—W. A. BOURNE, M.D., and J. K. WAGSTAFF, M.R.C.P.

Mrs. O., aged 56.

History.—Spring 1947, teeth suddenly decayed. A few months later, after severe emotional shock, she could not cry. Eyes have since felt dry and smarting, and vasomotor disturbance of hands has appeared. January 1948, following complete dental extraction, dryness of mouth, dysphagia for dry food, and intermittent hoarseness. March 1949, submaxillary and parotid secretions thickened and creamy, containing penicillin-sensitive cocci. No relief from penicillin. April 1950, atrophic rhinitis with ozæna.

Examination (November 1950).—Nasal and buccal mucosæ dry. Jelly-like exudate from parotid and turbid yellowish-grey fluid from submaxillary ducts. B.P. 180/100 mm.Hg. Mild atrophic vaginitis.

Investigations.—Salivation: volumes of saliva collected in five minutes after chewing fruit 0–2 c.c. (Control 7 c.c.) Pilocarpine 1/8 grain (8 mg.) subcutaneously caused profuse sweating but no salivation. Sialogram (parotid glands): Filling limited to main ducts, of normal size and uniform calibre.

Lacrimation: Schirmer's tests (control 45 min.) conjunctival stimulation, moistening extended 3 mm. along filter paper, nasal stimulation (ammonia) 5–7 min.

Gastric function: Alcohol and histamine stimulation produced volumes too small for quantitative estimation. Free acid present.

Pancreatic function: (positive dermal reaction to secretin) 2 c.c. resting duodenal contents aspirated per 30 min., 15 c.c. aspirated after mecholyl (25 mg. S.C.) in 80 min., volume probably low (average normal resting secretion 12·5 ± 5·7 c.c. in 20 min.; after urecholine 24·6 ± 12·3 c.c. in 20 min.) (Kyle *et al.*, 1950). Trypsin below normal, lipase increased, amylase normal. Glucose tolerance (low threshold glycosuria): Blood sugar mg.%, 155 at 1 hour, 182 at 1½ hr., 170 at 2 hr. Urinary diastase, output per 24 hours 5,760 (normal 8,000–30,000).

Blood: Hb 75%; R.B.C. 4,250,000. E.S.R. 46 mm.

Plastic sensitivity (onset after extraction suggested possibly due to plastic dentures): Negative.

Course.—Ozæna disappeared after local therapy and brief course of stilbœstrol. Vitamin A 150,000 units daily for a month has had no effect on oral condition.

Comments.—(1) Incomplete forms of the syndrome are probably not uncommon. In this case arthritis is absent, but there is vasomotor disturbance in the hands. (2) Co-existence of minor abnormalities in external pancreatic secretion, urinary diastatic excretion, and glucose tolerance, suggests pancreatic involvement. (3) Dryness of the mouth in this patient does not cause increased fluid intake.

REFERENCE

KYLE, G. C., *et al.* (1950) *Gastro-Enterology*, **16**, 285.

Mr. **Norman C. Tanner:** It has fallen to my lot to perform endoscopies on 4 or 5 cases of this disease. It is difficult to recognize œsophageal atrophy through an œsophagoscope, as I know of no accurate criteria for its diagnosis. Prior to examination the patients swallow a well-lubricated rubber stomach tube and in the cases of this disease which I examined the œsophagus appeared normally moist and of normal colour and size of folds.

Atrophy is usually diagnosed gastroscopically by thinning of the mucosal folds, by the ability to see the submucosal vessels through the thinned mucosa, and flattening or disappearance of the areæ gastricæ. Such an extreme form of atrophy did not appear to be a notable feature of the cases I observed, although in most the mucosa appeared to be of less than normal thickness, or with early atrophic changes. In one case an unsuspected gastric ulcer was found, the mucosa in this case being atrophic and gastritic.

Dr. F. Parkes Weber referred to findings in a paper by Dr. Philip Ellman, Dr. T. E. W. Goodier and himself, in the January number of the *Quarterly Journal of Medicine* (1951) **20**, 33.

Lipoid Pneumonia in a Case of Cardiospasm.—S. KENNY, M.D., D.M.R.D. (Introduced by NORMAN C. TANNER, F.R.C.S.).

H. C., female, aged 57. Para 2.

1934: Gradual onset of dysphagia.

1939: Cardiospasm diagnosed by Sir Arthur Hurst and patient given bougie treatment. At first she found it necessary to pass the bougie four times a day, but gradually found once a week was sufficient. She always lubricated the bougies with liquid paraffin.

Also, about 1939, she began to suffer from chronic constipation and for eleven years has been taking a wineglassful of liquid paraffin just before retiring at night.

During the past four years, she has had painful, swollen joints. This condition began in the small joints of hands and feet and spread to wrists, ankles, elbows, knees and shoulders. Because of the painful elbow and shoulder joints, the patient has had to sleep on her back.

22.5.50: Admitted to hospital following a hæmatemesis, which happened one day after she passed a bougie in the routine way.

13.6.50: Barium meal confirmed gross achalasia of the cardia (Fig. 1). Œsophagoscopy.

FIG. 1.—Showing achalasia of the cardia before operation.

FIG. 2.—(P.A.) Chest showing multiple shadows in both lower zones and hilar regions. Taken after operation.

22.8.50: Heller's operation (Mr. N. C. Tanner).

30.8.50: Patient on full diet.

27.10.50: Whilst screening to confirm the excellent clinical result (the œsophagus was practically empty seven minutes after swallowing barium), multiple dense opacities were noted in bases of both lungs.

X-ray films of the chest showed several, ill-defined, non-homogeneous opacities, some 2 cm. in diameter, in both lower lobes, especially towards the hila (Fig. 2).

Five weeks later, no change had occurred in the lung shadows. On questioning, the patient admitted a "loose cough", especially in the mornings during recent years, but it has definitely ceased since her operation.

The joint condition is interesting. X-rays show a minimal amount of joint damage, despite clearly punched-out areas, especially in the heads of phalanges and distal ends of ulnæ,

with comparatively marked soft-tissue swellings. Further, there are multiple tophi-like swellings over both elbows and second metacarpophalangeal joints.

Though there has been no biopsy made in this case I think it is comparable to proved cases of lipoid pneumonia as described by Ikeda (1937) and Santé (1949).

For some eleven years, this patient's gross achalasia and nocturnal dose of liquid paraffin together provided a constantly full "well" of this fluid, because the light liquid paraffin floated on top of the other food contents and "toppled" over into the trachea. Thence it passed to the bronchus, where in Santé's words, it formed a "plastic foreign body" which was sucked into the alveoli as the air was absorbed from them, and whence no ciliary action or cough reflex could remove it. As liquid paraffin cannot undergo saponification, it was eventually carried off by the phagocytes to the interstitial lymphatics. There followed an extreme degree of reaction, resulting in fibrosis and dense, almost acellular, scar tissue.

Masses of paraffin droplets, meshed in heavy scar tissue, give rise to paraffinomata resembling pneumoconiosis, but the main distribution of the two conditions is different. However, the similarity of the two pathological processes seems to suggest that some name such as "paraffinosis" should be given to the condition of lipoid pneumonia. This might help to draw attention to the dangers of liquid paraffin addiction. The Americans have already pointed out the danger, but perhaps liquid paraffin addiction is commoner in America (Thomas and Jewett, 1926).

The patient, cured of her dysphagia, is also finding gradual but definite relief from her rheumatic symptoms. She is now able to carry out small household tasks after three years' exemption from such duties.

Whatever the common psychogenic basis for achalasia and the rheumatoid conditions, it is interesting to see such a marked improvement in the latter condition in a patient, just four months after she has been successfully treated by surgery for the former condition.

NOTE.—The second case of lipoid pneumonia reported post mortem in an adult was that of a man aged 32 who had suffered from achalasia of the cardia for four years (Ikeda, 1937).

REFERENCES

IKEDA, K. (1937) *Arch. Path.*, **23**, 470.
SANTÉ, L. R. (1949) *Amer. J. Roentgenol.*, **62**, 788.
THOMAS, W. S., and JEWETT, C. H. (1926) *Clifton med. Bull.*, **12**, 130.

[*January* 12, 1951]

Multiple Myelomatosis (Plasmacytoma Type) First Diagnosed in 1936 and Showing an Unusual Distribution Culminating in Cutaneous and Muscular Deposits.—R. T. CAMPBELL, F.R.C.S. (for A. DICKSON WRIGHT, M.S.).

K. A., male aged 45. Philatelist.

First noticed pain in back in 1934, which increased until 1936 when he gradually developed a spastic paraplegia for which he was referred to the Maida Vale Hospital in May. X-ray showed a destructive lesion of T 8.

13.6.36: *Laminectomy* (Mr. A. Dickson Wright).—Cavity in body of T 8 full of friable growth compressing cord extradurally; curetted. Biopsy report: plasmacytoma (Fig. 1).

Costotransversectomy (Mr. A. Dickson Wright).—Further removal of tumour and insertion of 20 radon seeds.

Following these operations his paraplegia gradually recovered completely and he was back at work in November 1936.

June 1937, following pain in right side of pelvis, X-ray (Fig. 2) showed a large area of bone destruction in the right ilium. Good response to X-ray therapy. Remained well until May 1942 when further X-ray treatment was given to the dorsal spine for recurrence of dorsal backache.

June 1943, recurrence of paraplegia. Further laminectomy (Mr. A. Dickson Wright) and removal of tumour, followed by X-ray therapy. Recovery, but with residual spasticity.

May 1945, following recurrence of dorsal backache, re-explored by Mr. Dickson Wright and a further mass of extradural plasmacytoma removed.

X-ray therapy to thoracic spine (Fig. 3) at intervals until October 1948, since when this lesion has become quiescent.

March 1949: Cutaneous deposit above umbilicus. Biopsy—plasmacytoma. Disappeared with X-ray therapy.

September 1949: Cutaneous deposit left thigh. Disappeared with X-ray therapy. Deposit right upper femur and lower end right fibula.

December 1949: Tuberculous right epididymis. February 1950: X-rays showed calcification and healing of original lesion in pelvis (Fig. 4). Deposit in lumbar spine. March 1950: Deposit in skin of left buttock. Excised: plasmacytoma. June 1950: Exophthalmos left eye, ? orbital deposit. Rapid resolution with X-ray therapy. December 1950: Muscular deposits, left thigh, right thigh, and right calf. Right calf deposit excised and showed plasmacytoma within muscle (Figs. 5, 6).

Biochemical findings.—Bence Jones protein present in urine on several occasions, in 1950 and 1951.

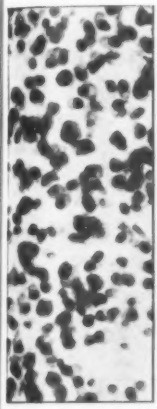


FIG. 1.—1936: Deposit in body of T8. (H. and E. × 400.)

FIG. 5.—1950: Deposit in R. calf muscle. (H. and E. × 112.)

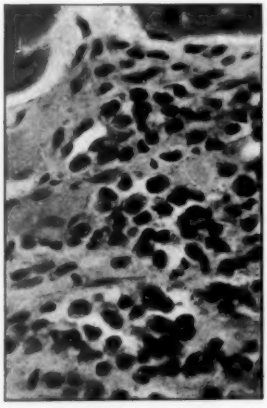


FIG. 6.—High power of Fig. 5. (× 400.)

FIG. 3.—1947.

FIG. 2.—June 1937.

FIG. 4.—February 1950.

B.S.R. 92 mm. in the first hour, January 1951.

Plasma proteins 7·6%. Alb. 5%: Glob. 2·6%.

Estimation of globulin fractions showed enormous decrease of gamma globulins, and marked increase of alpha globulins.

This case appears to be the longest recorded survival of multiple myeloma, having lived sixteen years from onset of symptoms. The distribution of deposits has been unusual, and reports of cutaneous deposits are rare. I can find no record of deposits in muscle. The lesions have also been very radiosensitive.

Left Recurrent Laryngeal Nerve Paralysis Due to Dilatation of the Pulmonary Artery in a Case of Bronchitis and Asthma.—A. POTELIAKHOFF, M.D. (for B. GOTTLIEB, M.D.).

M. J., female, aged 54, was admitted to St. Mary Abbots Hospital in August 1948 in status asthmaticus. Her voice had been hoarse for three months.

Past illnesses.—Recurrent bronchitis since childhood. Asthma since age 18. Pneumonia in 1946. Recurrent laryngeal nerve palsy first noted in June 1948.

On examination.—Kyphotic. Signs of bronchitis, asthma and emphysema. B.P. 240/140. Apex beat 4 inches from mid-line. No murmurs.

X-ray (Fig. 1) confirmed clinical findings and showed enlargement of the pulmonary conus. The left ventricle was not obviously enlarged and the cardiothoracic ratio was 11·5 : 24.

FIG. 1.—Dilatation of pulmonary conus.

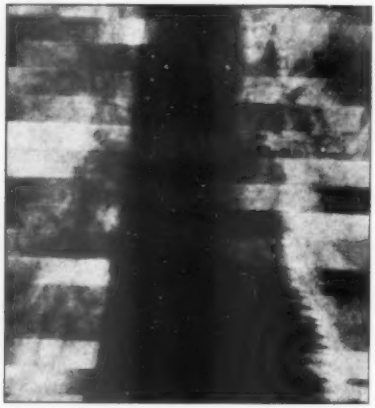


FIG. 2.—Pulsation of conus and pulmonary arteries.

Other investigations.—There were no tubercle bacilli or malignant cells in the sputum Eosinophilia 16%. Laryngoscopy confirmed the left vocal cord paralysis. This finding was at first explained on a basis of neoplasm at the left hilum and bronchoscopy, by demonstrating a narrowing of a stem bronchus, supported this view.

A year later she had put on weight and, during the interval, she had been free from asthma. The diagnosis of neoplasm had to be revised.

On screening the pulmonary conus and the dilated pulmonary vessels were seen to pulsate. A kymograph (Fig. 2) confirmed the hilar dance. Her vital capacity was 1,500 c.c., i.e. 50% of normal. Chest expansion was 1½ in.

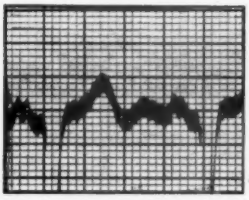


FIG. 3.—One complex of CR4 demonstrating the bifid P wave.

E.C.G. (Fig. 3) showed a bifid P wave and right axis deviation suggesting pulmonary hypertension. Blood W.R. and Kahn were negative. Finally barium swallow and X-ray in the R.A.O. position showed no enlargement of the left auricle.

Comment.—Paralysis of the left recurrent laryngeal nerve has been described in several cardiac conditions. Thus it is known to occur in mitral stenosis, in hypertension, in aneurysm of the aorta and in some forms of congenital heart disease. In these conditions the responsible factors may be enlargement of the left auricle, dilatation of the pulmonary vessels, or dilatation of the aorta.

Fetterolf and Norris (1911) discussed the mechanism. They postulated that the nerve was compressed between the pulmonary artery and the aortic arch and was prevented from escaping by the ligamentum arteriosum. King *et al.* (1934) added the concept of the dynamic dilatation of the pulmonary vessels at each pulse-beat and later Dolowitz and Lewis (1948) described how the nerve could, on occasion, be fixed by inflammation and fibrosis of small glands in its neighbourhood. In all the cases reported a primary cardiovascular pathology was noted.

More recently Brinton (1950) reported a case of vocal cord paralysis secondary to primary

pulmonary hypertension, thought to be due to an anastomosis between the bronchial and pulmonary arteries.

In the case here reported there is no primary cardiovascular disease to account for the pulmonary hypertension. Systemic hypertension exists but has not given rise to left auricular enlargement.

No previous reference has been found to vocal cord paralysis in cases of asthma associated with cor pulmonale. In 15 autopsied cases of asthma reported by Schiller *et al.* (1943) there is no mention of it. 4 of these cases had cor pulmonale and right heart failure.

The view is put forward, on the basis of this case, that pulmonary hypertension, secondary to bronchitis and asthma, can lead to left recurrent laryngeal nerve paralysis.

REFERENCES

BRINTON, W. D. (1950) *Brit. Heart J.*, **12**, 305.
DOLOWITZ, D. A., and LEWIS, C. S. (1948) *Amer. J. Med.*, **4**, 856.
FETTEROLF, G., and NORRIS, G. W. (1911) *Amer. J. med. Sci.*, **141**, 625.
KING, F. H., HITZIG, W. M., and FISHBERG, A. M. (1934) *Amer. J. med. Sci.*, **188**, 691.
SCHILLER, I. W., *et al.* (1943) *New Eng. J. Med.*, **228**, 112.

Suprarenal Tumour.—T. M. D. GIMLETTE, M.B., B.Chir., and H. J. C. SWAN, M.R.C.P. (for J. S. RICHARDSON, M.V.O., M.D.).

J. McG., aged 41.

Admitted 2.10.50 into St. Thomas's Hospital with a history of hypertension for seven years, discovered at routine examination. He had suffered from sudden attacks of pallor with sweating of the face and hands, when excited or anxious, since the age of 16. More recently he complained of slight tiredness and breathlessness and occasional headaches; he had a transient right arm monoplegia and aphasia a week before admission.

On examination, B.P. was found to be 240/140, there was some left ventricular enlargement, the retinal vessels were normal, trace of albuminuria, renal function otherwise normal. I.V.P (Fig. 1) showed downward displacement of left kidney by a mass containing calcified

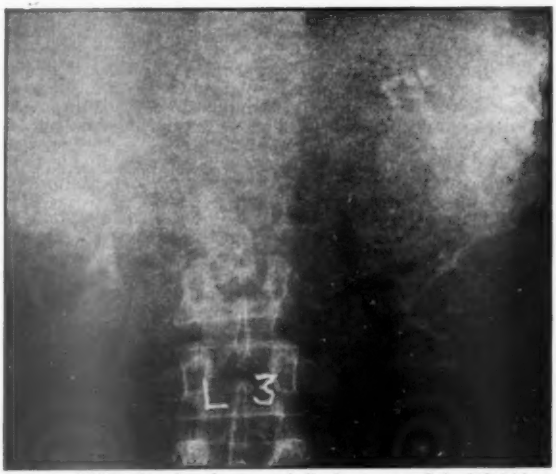


FIG. 1.—I.V.P. showing downward displacement of the left kidney by a mass which contains a group of calcified opacities.

opacities. B.P. varied while in bed, generally about 190/110, the lowest level recorded was 160/95. Under the influence of sodium amytal a sharp rise in B.P. to 235/135 occurred while the patient was deeply asleep. He also had persistent tachycardia and slight pyrexia while in the hospital before operation.

At operation for left thoracolumbar sympathectomy on 16.10.50 by Mr. R. H. Boggon a tumour of the left suprarenal about 3 in. in diameter was found. B.P. rose to 300/180 on manipulating this, after its removal B.P. fell to 70/50. Intravenous noradrenaline was given

for the next three hours, after which time B.P. became stabilized at about 120/90 and subsequently remained at about 140/90 until discharge from hospital on 4.12.50. It is suggested that noradrenaline as used in this case may help to make successful a difficult operation. Recovery was delayed by paralytic ileus, deep vein thrombosis in the left leg and wound infection with development of a sympathetic left pleural effusion.

The tumour, which weighed 350 grammes, was found microscopically to be a phæochromocytoma of the adrenal medulla; analysis showed it to contain 85 micrograms of adrenaline and 825 micrograms of noradrenaline per gramme of tissue. There was an area of mucoid degeneration and calcification in the tumour.

On 31.1.51 the blood pressure was 145/90 after lying down.

Comment.—This case shows certain features suggestive of phæochromocytoma as the cause of a fixed hypertension, particularly in the attacks of sweating and pallor, the rather labile B.P. with its unexpected rise under sodium amytal, the tachycardia and slight pyrexia, and the abnormal X-ray.

Besides the features described above, there are a number of investigations which may be useful to help establish the diagnosis, particularly if as many as possible of them are done in likely cases, so that their value can be more clearly assessed with further experience.

(1) The cold pressor test often fails to show a rise in B.P. in the presence of a phæochromocytoma.

(2) Postural hypotension is frequently present.

(3) The benzodioxone test; this substance is used as an adrenergic blocking agent, causing a fall in B.P. if the hypertension is due to circulating adrenaline or noradrenaline from a secreting tumour.

(4) Estimation of renal pressor substances in the urine is useful if the necessary facilities are available.

(5) Metabolic rate and blood sugar studies may give indications of higher metabolism.

The prospects of successful surgery are now such that it has become important to investigate each hypertensive carefully to find the few in whom the presence of a phæochromocytoma offers a bright hope of cure.

Dr. A. Elkeles: Dr. Richardson's case showed a calcified opacity above the left kidney, which brings to my mind a similar case presented at this Section three years ago as a probable tuberculoma of spleen and benign hypertension. This patient, a male aged 44, had an accident in 1940, in which he fractured his left lower ribs. In 1947 when he complained of tightness in upper abdomen, a mass could be felt below the left costal margin, which was considered to be a large spleen. His blood pressure was 240/100. Radiographs of abdomen showed speckled calcifications and calcified cyst-like shadows in left upper abdomen. I.V.P. was normal but there was slight downward displacement of the left kidney. During the discussion I suggested that the calcified shadows might be the result of subcapsular hæmorrhage of the spleen, caused by the patient's severe injury to the left lower chest wall.

By chance I heard of this patient, when he was readmitted to hospital in 1950. The mass in the left upper abdomen had grown considerably. An operation was performed and a large calcified suprarenal tumour was found.

It is probably more than a mere coincidence that in Dr. Richardson's as well as in this case calcification above the left kidney was seen in suprarenal tumours. It is, therefore, suggested that calcifications seen in the left or right upper quadrant of the abdomen, when associated with hypertension, may be of value in the diagnosis of suprarenal tumours.

Shortly after the last clinical meeting I came across a report of a case showing calcification in the right upper quadrant of the abdomen, simulating cholelithiasis. At necropsy a phæochromocytoma of right adrenal gland, showing circular calcification within the tumour, was found (Moser, M., Sheehan, G., and Schwinger, H. (1950) *Radiology*, **55**, 855).

Unilateral Fused (Sigmoid) Kidney.—G. Qvist, F.R.C.S.

Male, aged 64. Bleeding *per rectum.*

Examination shows small mass to left of umbilicus. Investigation shows the mass to be both kidneys lying to the left of the spine.

Barium enema normal. Bleeding due to hæmorrhoids.

Operation hæmorrhoidectomy April 1950.

January 1951 no symptoms.

Retrograde pyelograms show right kidney lying below the left, to left of mid-line.

Cystoscopy shows both ureters opening normally into bladder.

Section of Ophthalmology

President—M. L. HINE, M.D., F.R.C.S.

[*November* 9, 1950, *continued*]

DISCUSSION ON SCLERAL RESECTION AND CHEMICAL COAGULATION OPERATIONS FOR RETINAL DETACHMENT

Mr. A. Lister: The majority of so-called idiopathic retinal detachments are cured by diathermy. There is, however, an appreciable proportion of cases in which the response to diathermy is unsatisfactory. The purpose of this paper is to discuss certain alternative methods of treatment for these cases, which methods seem to hold a better chance of success than diathermy.

The group of cases in question includes the following:

(1) Aphakic eyes.

(2) Gross retinal degeneration, either senile or myopic, associated with multiple or very large tears.

(3) Traumatic detachments in which there are organized bands in the vitreous.

(4) Detachments of long standing.

(5) Detachments in which previous diathermy has been unsuccessful, a fresh tear having occurred at the edge of or near to the diathermy scar. In these cases the retina over the diathermy scar commonly has a thin cobweb-like appearance which, to my mind, spells inevitable failure for further attempts at diathermy.

The high proportion of failures after diathermy in these cases seems to be due to one or more of the following causes:

(1) The retina is so atrophic that shrinkage of the diathermy scar leads to further tearing.

(2) The retina is held away from the choroid either by organized bands, by shrunken adherent vitreous or by vitreous attached to a corneal scar.

(3) The retina has shrunk.

Assuming that the explanation of the mechanism of these unsatisfactory detachments is correct their treatment presents two problems:

(A) For those cases in which the retina is mechanically incapable of reattachment: to overcome this by reducing the size of the globe.

(B) For those cases in which the retina is very atrophic: to produce a wide area of choroido-retinal adhesion which will not shrink.

It may be an advantage in some instances to combine these two methods of treatment.

(A) *The size of the globe is reduced by scleral resection.* This operation was introduced by Müller in 1903. It was more successful than other methods of that period but it disappeared with the advent of Gonin's ignipuncture. It was revived by Lindner in 1933 and it is largely his technique which is followed to-day. Gayer Morgan successfully resected a scleral staphyloma in 1943 but the first resection for detachment performed in England was, so far as I know, in the summer of 1947 and the patient was an ophthalmic surgeon—a patient of Mr. Juler's.

As regards results, among 121 cases collected from the literature by Leopold in 1945 (reported in the discussion on Pischel's paper 1945) there were 25 successes. Borley (1949) reported 9 successes in a series of 28—some with and some without diathermy in addition.

My own results are shown in the accompanying table.

TABLE I.—RESULTS OF RETINAL DETACHMENTS TREATED BY SCLERAL RESECTION

Etiology	No.	Cured	Improved	Failed
*Senile aphakia	8	2	2	4
*Congenital aphakia	5	1	—	4
Total	13	3	2	8
Myopia	11	3 (1 recent)	1	7
Sundry	10	5 (Vision not improved in 2)	—	5
Grand total	34	11 (33%)	3	20
Not previously diathermied	13	6		
Previously diathermied ..	21	5		

*i.e. Aphakia following senile or congenital cataract operation.

(B) *The second problem, that of producing a more gentle reaction and a scar which has less tendency to contract than that of diathermy* is met by employing a chemical method of coagulation, the chemical used being caustic potash. This method was invented by Guist in about 1930 and was adopted particularly by Lindner. It is known either as the Guist or Lindner-Guist operation. As is well known Guist's operation consists of surrounding the area covering the retinal tear with multiple trephine holes in the sclera, and touching the exposed choroid with solid caustic potash, which is neutralized at once with acetic acid. In order to reduce the number of trephine holes Lindner introduced a modification by which a spatula is passed between the trephine holes so as to make a subscleral tunnel. Potash (6%) was injected along the tunnel.

The results were quite good—about 50% successes. Taken as a whole, however, they were not as good as those of diathermy and the method has certain disadvantages which have limited its popularity. Firstly it is impossible to place trephine holes even as far back as the equator; secondly, if the choroid is accidentally punctured before the ring of holes is complete, the operation usually has to be abandoned. Thirdly the operation is extremely tedious. Gonin quoted Lindner as describing it as "la plus fatigante et la plus difficile de notre specialité".

In spite, however, of its disadvantages I suggest that the operation is preferable to diathermy in certain cases and that, though it can never be easier, technically, than diathermy it can be made considerably easier than it was in its original form.

This can be done in one of two ways, (*a*) by trephining only one hole and injecting through it 3% (or possibly weaker) potash over the required area of choroid with a lacrimal syringe or (*b*) turning back a flap of sclera and painting 3% potash on the choroid.

Of the eyes treated by Guist's method (original or modified) 5 out of 6 have been successful.

The following is a sample of cases successfully treated by scleral resection or Guist's operation, or a combination of the two. In fact in cases of simple resection I always paint the exposed choroid with 3% potash before sewing up.

Figs. 1 to 3 refer to a low myope aged 49; two months' history; unsuccessful diathermy. Vision seven months after operation = 6/18.

Figs. 4 to 6 refer to an aphakic of 55; congenital cataracts needled in childhood; right detachment of 9 months; no hole. Vision four months after operation = 6/24. Refraction changed from +3 to +8 D.

Figs. 7 to 9 refer to an emmetrope of 65; detachment in amblyopic eye.

Fig. 10 refers to myope of 64, monocular. Vision one year after operation 3/60; retina in place.

One other case was of special interest; an aphakic detachment was apparently cured by resection. Two months later, however, a shallow detachment developed in the macular area due apparently to adherence of vitreous to the scar of a paracentesis wound made during the resection. Division of this adhesion did not cure the second detachment which, however, remained localized.

I hope an impression has been created that the operations discussed are of real value, not merely as auxiliaries to the usual methods of treatment but as primary operations.

REFERENCES

BORLEY, W. E. (1949) *Trans. Amer. ophthal. Soc.*, **47**, 462.
PISCHEL, D. K. (1945) *Trans. Amer. Acad. Ophthal. Oto-laryng.*, **49**, 155.

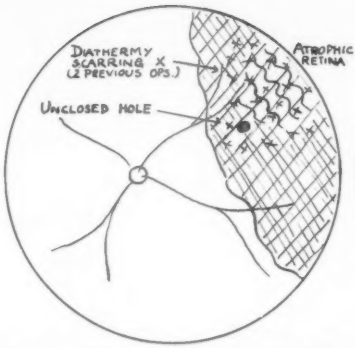


FIG. 1.—Detachment prior to resection.

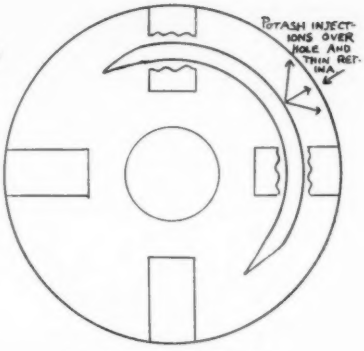


FIG. 2.—Area of resection.

FIG. 3.—Same case as Figs. 1 and 2.

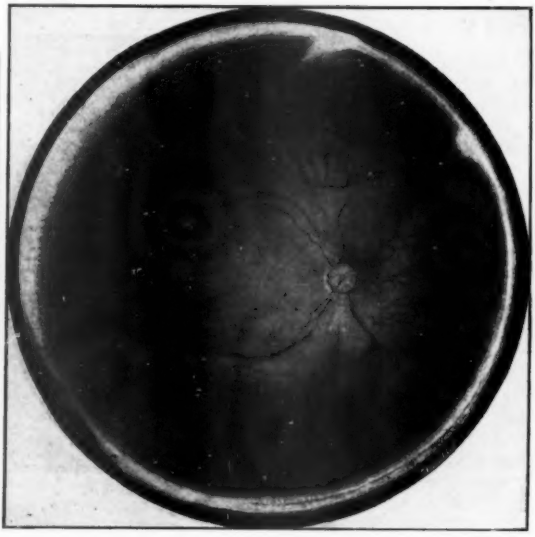


FIG. 6—Same case as Figs. 4 and 5.

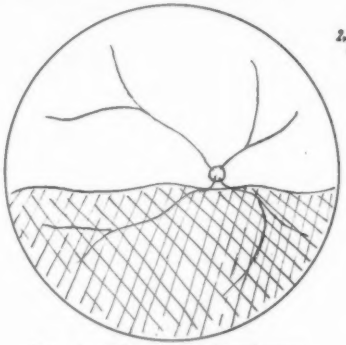


FIG. 4.—Diagram of detachment.

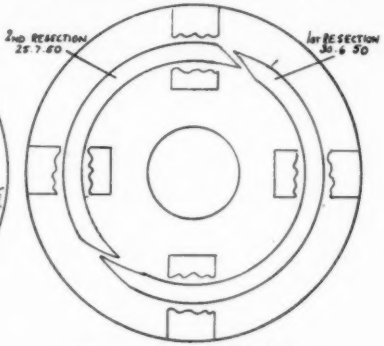


FIG. 5.—Area of resections.

Mr. A. Lister (*see text p.* 414).

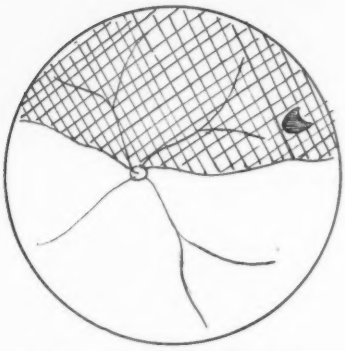


FIG. 7.—Diagram of detachment.

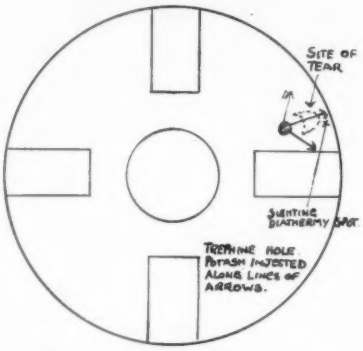


FIG. 8.—Modified Guist's operation.

FIG. 9.—Same case as Figs. 7 and 8. (Fundus painting by P. Archer)

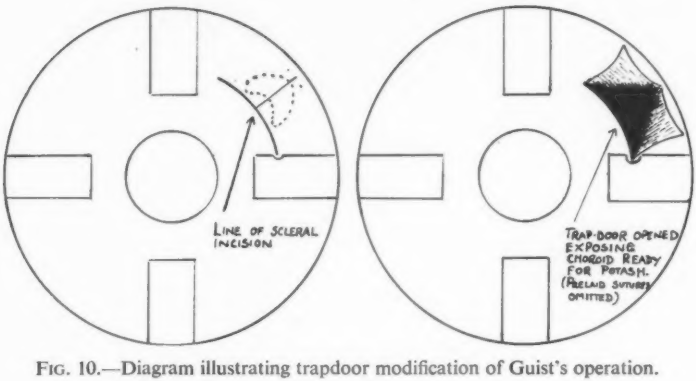


FIG. 10.—Diagram illustrating trapdoor modification of Guist's operation.

Mr. A. Lister (*see text p.* 414).

Mr. **A. Seymour Philps:** In presenting this paper on scleral resection I propose to reverse the usual procedure and begin with results, so that we can judge if the operation is of any use. After that, I will discuss selection of cases, and go on to consider difficulties and complications, in order that we may be able to assess the danger of the operation.

Results.—Table I shows the results in the 19 scleral resections up to the middle of 1950.

TABLE I.—RESULTS IN 19 CASES OF SCLERAL RESECTION

Refraction	Number of cases	Cures
Emmetropes	5	3½
Myopes	7	2
Aphakics	7	6
Total	19	11½

By "cure" is meant that the retina has been totally replaced and unless this is so the case is classed as a failure. The "half-cure" under "emmetropes" does not mean that half the retina was replaced, but is calculated as follows: The girl in question had a disinsertion which ran half-way round the globe. Diathermy failed to reattach the retina and scleral resection was tried. This reduced the detachment to small proportions, leaving only one area below which was not flat, and to this area diathermy was applied subsequently with full restoration of the retina to its bed. In the light of later experience it seems that this might have happened even without the final operation.

Aphakics.—The most successful group were the aphakics, all having had the extra-capsular operation, except two who had had cataracts needled in infancy, and in all of whom the hole was hidden from view by capsule. The only failure could have been avoided by more careful selection of cases, for a man who had bilateral aphakic detachments had the first retina replaced, and, spurred on by this and by his own wishes, I operated upon the second eye. The detachment in this eye was total and I now know that the operation in such a case was doomed to failure from the start.

In all the aphakic cases but one the patient had had previous diathermy operations—sometimes as many as three. These diathermies were done elsewhere, and I would now say definitely that for me the resection operation is the operation of choice in this condition. The one patient who came directly under my care without any previous treatment was shown here tonight.

Emmetropes.—All the patients in this section were young people, the oldest being 24 and the youngest 8. Of the 5 cases 2 were traumatic and 3 complications of Eales's disease, the latter all having bands in the vitreous. Two of these Eales's disease eyes belonged to a boy of 8, who is now at a normal school in India. The other Eales's disease case had two resections and the retina was restored except for one area where the retina was pulled up in a tent-like cone by a band of tissue in the vitreous. I did consider the possibility of dividing this band, but felt it was too hazardous. Unfortunately, the band continued to contract and this boy's retina was subsequently pulled off again completely, and as this was in his only eye he is now blind.

Myopes.—This was the least successful group, only 2 cures out of 8 cases; one of the cures being shown here tonight. Most of these were very bad cases, with thick vitreous haze and almost complete detachments. Each had had diathermy before—sometimes three times. The average refraction of the whole group was – 12·0; individuals varying between – 3·0 and – 22·0. For these high myopes, scleral resection is not enough and perhaps the answer lies in combining it with some form of chemical coagulation.

Indications.—The only indication so far has been an eye with a detachment which could not be restored by other methods. In 12 of the 19 cases, the patient's other eye was blind and in such patients the indication is clear and the surgeon's advice readily accepted. In those who have another seeing eye and who have perhaps already spent months in hospital, much must depend on the age of the patient.

The time the detachment has been present varies enormously, from four weeks in the one case in which the operation was done from choice, to something like ten years in the case of the London navvy you saw here tonight. In such cases, while the retina may be restored to its bed it is usually not viable—as can be seen by looking at the optic disc—and, therefore, the field of vision is not improved by the operation, although the eye may be made safer by it.

Contra-indications.—For the operation to succeed there must be some point at which the retina is still attached. Total umbrella detachments do not respond to this, or to any other, operation. Dense bands in the vitreous also militate against success.

TECHNIQUE

It will be sufficient to emphasize some important points:

Anæsthesia.—Except where the patient is a child, this is always local: lid infiltration, facial nerve block, retrobulbar injection above and below the palpebral fissure.

Exposure.—The widest possible palpebral fissure is necessary for this operation. To this end the surgeon should begin with an external canthotomy which, coupled with a facial nerve block, will give all the room required. Assuming that 180 degrees of the globe is to be resected at least one rectus muscle needs to be detached from its insertion, and sometimes two. These measures, coupled with traction sutures inserted into the sclera, will enable the eye to be retracted in the required direction so that the sclera can be exposed up to 17 mm. behind the limbus. Finally the surgeon takes a cautery point and arrests all bleeding points so that he has a clear view of a dry field.

Amount of the resection.—Before an eyeball can be materially reduced in size, it is necessary that some of its contents should be removed, otherwise no reduction is possible. In scleral resection the only content removed is the subretinal fluid and the eye can be reduced by the amount of the subretinal fluid and no more. To some extent the surgeon can estimate the amount of his resection by knowing the amount of subretinal fluid present, and indeed Lindner claims to be able to forecast his resection in millimetres by this means. Personally, I mark out a strip 10 mm. from the limbus and 3–4 mm. wide, which can be altered if necessary in the light of after-events, depending upon how much S.R. fluid escapes. The subsequent steps of raising the scleral strip are best demonstrated by drawings (Fig. 1). Once the subretinal fluid has been evacuated the rest of the resection is straightforward and the strip can be widened a little if much fluid is evacuated.

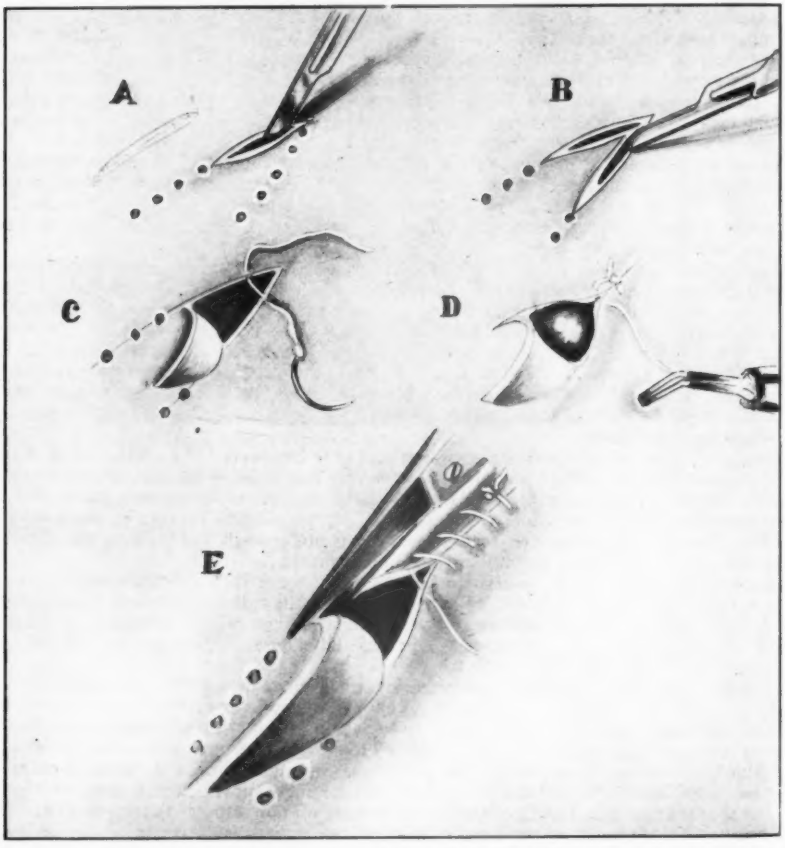


FIG. 1.—A, The beginning of the scleral resection—incision of the sclera down to choroid with a small Bard-Parker or Gillette knife, the strip having previously been marked out with a cautery. B, Continuing the incision of the sclera until a tag of sclera can be raised at one end of the resection. C, Insertion of the first suture, which is then tied. D, Cautery puncture into an area away from the resection to allow subretinal fluid to escape and the choroid to sink back within the globe. E, Continuing the resection with scissors.

Complications during the operation.—The only fluid which should escape from the eye is subretinal fluid. If vitreous does so, that is a complication. Amongst other effects it defeats the purpose of the operation. It is unlikely to happen where the choroid is normal, but most of these patients have had diathermy operations before and in certain areas the choroid will have been "blasted" until it no longer exists. When the surgeon approaches such an area, greater care is needed. The suprachoroidal space is obliterated and once sclera has been divided nothing but retina—sometimes very atrophic—lies between him and the vitreous. With care, and following up his scissor cuts ever more closely with the stitch, this complication of vitreous loss can be avoided.

Pricking the choroid with the needle and so causing it to bleed is a minor accident which is also better avoided.

Apart from these, I have not met any complications during the operation.

Complications after the operation.—In my experience this is not a dangerous operation.

Only 2 patients in this series have had any complication at all. The first concerns the second eye of a man whose first retina had already been restored to its bed. The second eye was totally detached, but, spurred on by the patient and by my own inclinations, I operated on this eye too. The retina did not go back and he left hospital with a total detachment still present. Some few months later this second eye became inflamed and painful with acute iritis and rise of tension, such as we all meet in eyes where the retina is totally detached. His wife was an ophthalmic surgeon and, not wishing to have anything whatever upsetting his left eye, with which he could see to read, she had the inflamed eye removed. This eye I had sectioned and it showed total umbrella detachment and acute uveitis. This is the only eye that has been removed in this series and I think we can agree that it was part of the course of the disease and not influenced by operation.

One other complication has arisen. A woman (Mrs. L.), whose second eye detached after the first had become blind, had, after a long interval, a scleral resection. She also suffers from congestive heart failure and a high venous pressure. This lady, although fundus examination was satisfactory one week after operation, had a total vitreous hæmorrhage three days later. That was only two weeks ago and I can say no more about her at present. Her light projection is still accurate.

These are the only complications so far. To the question—Have you made anyone worse? I have to answer "Yes", Mrs. L., who saw 2/60 on admission and now has only light perception. But there seems a good chance that in time she may be better.

Vision after operation.—This is, of course, determined by the extent of the detachment before operation, but a chart of the successful cases may be of interest (Table II).

TABLE II.—VISION AFTER OPERATION

6/9	6/12	6/18	6/24	6/36	6/60	5/60	4/60	3/60	2/60
1	3	1	2				2	1	1

Delay before operation.—It is doubtful if long delay before operation influences the outcome, but it certainly is a fact that the longer the delay the worse the visual result. The detached retina carries its blood vessels with it and for a time it survives. Later it becomes transparent, especially in long-standing detachments. Once this has occurred, although the retina may still be restored to its bed, the field of vision does not improve. The retinal atrophy shows itself in the secondary pallor of the disc, as you may have seen in J. T., shown here tonight (Table III).

TABLE III.—DELAY BEFORE OPERATION

5–10 yrs.	2–5 yrs.	1–2 yrs.	6–12 mths.	3–6 mths.	under 3 mths.
J. T.	R. S.	R. S.	R. S.	R. McK.	H. C.
	E. B.		R. L.	H. G.	E. D.
				G. P.	

Finally, all who have done this operation will, I hope, have been impressed with the absence of reaction afterwards—less in fact than after diathermy. One is amazed, after a difficult and severe operation, to find a few days later that the eye is almost white and there is little or no swelling. This only illustrates the fact that cutting produces less damage than diathermy, and that operations on the posterior segment of the eye, which completely avoid the ciliary area, are very well tolerated.

Mr. C. Dee Shapland: *Scleral resection—lamellar.*—It is interesting and encouraging to look back on the gradual evolution of the treatment of simple detachment of the retina in the past twenty-five years. When I first joined the practice of Moorfields as a junior assistant early in 1927 such cases were not even admitted to the wards and for the very few that were the treatment either consisted of prolonged rest in bed in double pads and head immobilized between sandbags or surgically of a cautery puncture over the deepest part of the detachment. The percentage of repositions by these means is not known but must have been very small, indeed in an article in the *Lancet* (1929) it was stated that "there are few ophthalmic surgeons who cannot count on the fingers of one hand the cases of cure of detached retina within their own personal experience".

Gonin's work changed all this and at Moorfields from the end of 1929 onwards the percentage of successes rose to about 30 for the Gonin cautery puncture and for the Guist multiple trephining operations, rising to some 45% in the early years of the various types of diathermy operation. This figure has been appreciably improved upon since the last war, my own figure for 1948 being 67·9% of repositions in 28 cases. Nevertheless the cures by the diathermy operation have levelled off at about 70%, so that some 30% of cases are doomed to be failures by this method.

TABLE I.—PERCENTAGE REPOSITIONS IN THE REFRACTIVE GROUPS (SERVICE AND CIVILIAN)

Hypermetropia and emmetropia	60 eyes (75·0%)
Myopia, under 5 D	34 eyes (67·6%)
Myopia, 5–10 D	32 eyes (50·0%)
Myopia, over 10 D	27 eyes (40·7%)
Aphakia	11 eyes (36·4%)

It is clear from these figures (Table I) taken from my paper on "Prognosis in Detachment of the Retina" (1948) that it is in the higher grades of myopia and in the aphakic eyes that the least satisfactory results are obtained, or regarding the case from the type of retinal defect (Table II) the outlook is worst in detachments with giant and irregular rents and in those in which no hole can be discovered.

TABLE II.—PERCENTAGE REPOSITIONS CORRELATED WITH THE VARIOUS TYPES OF RETINAL DEFECT (SERVICE AND CIVILIAN)

Peripheral dialyses (excluding giant dialyses)	48 eyes (83·3%)
Round, oval and fenestrated areas	35 eyes (68·6%)
U-shaped and radial slit rents	56 eyes (53·6%)
Giant and irregular (including giant dialyses)	12 eyes (25·0%)
No holes found	13 eyes (15·4%)

These are, in effect, almost synonymous statements as in general it is the detachment in the high myope with atrophic retina which presents with the giant, irregular or multiple defects whilst it is the detachment occurring in the eye rendered aphakic by discission or by an extracapsular extraction which produces the majority of the "no hole" cases.

I therefore performed my first scleral resection on May 16, 1949, on the right eye of a high myope of 47 years whose left retina had detached in June 1944 and had been operated upon twice by a senior colleague at Moorfields, but without success, and whose right retina detached in October 1948 and had been operated upon twice by me in that and the following month by diathermy also without success, secondary tears forming behind the surface applications. Although the retina was not completely replaced by the scleral resection which was performed temporally from 6–12 o'clock, he and I have been quite pleased with the result as the retina is now only shallowly detached, no complicated cataract has developed as yet and central vision with correction remains at 3/60. I was therefore encouraged to continue with this operation in cases of failure with diathermy and to date I have operated upon 15: 7 myopes, 6 aphakics and 2 emmetropes. In 3 cases I have performed a scleral resection of the whole circumference of the globe and, as I have not yet done more than half the circumference in one stage, 18 separate operations of this nature have been performed to date.

All but one of them have been performed on failures by the diathermy operation and as I found the separation of choroid from sclera in the plane of the suprachoroidal space difficult at the site of previous surface diathermy reactions, I have, since July 1949, performed what I have called a "lamellar scleral resection". In this operation I remove a strip of sclera from half the circumference of the globe, in depth just short of the suprachoroidal space, so that a very thin film of the deepest scleral lamellæ, of tissue paper thickness only, is left on the surface of the choroid at the site of the resection (Fig. 1).

The operation which I demonstrated at the International Congress on July 17, 1950, is performed under general anæsthesia and takes about an hour. The conjunctiva and

Tenon's capsule are opened over the site of the planned resection which should be centred on the defects or suspected defects in the retina. Suppose a temporal half-resection is being performed. The external rectus is divided after two whip sutures of 000 catgut have been placed in its upper and lower borders 2 mm. from its insertion and a retraction suture of No. 1 white silk is inserted in its stump. The exposed and cleaned sclera is marked by a touch of the cautery at points 10 mm. behind the limbus at the lateral border of the inferior rectus, lower border of the external rectus, upper border of the external rectus and lateral border of the superior rectus. Two further cautery marks are made 4 mm. behind those at the upper and lower borders of the external rectus (Fig. 2). A Maddox needle threaded with

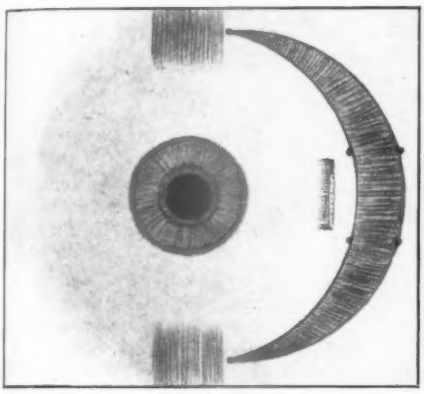


FIG. 1.—Strip of excised sclera averages about 30 mm. in length. Width as planned.

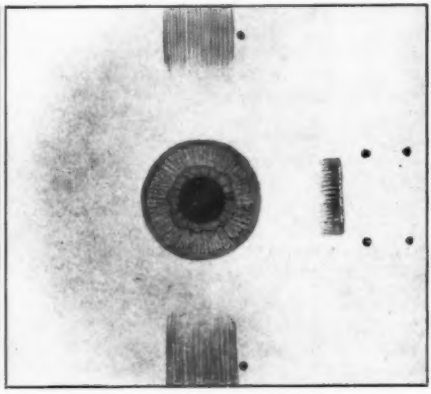


FIG. 2.—Cautery marks on exposed and cleaned sclera, 10 and 14 mm. behind limbus.

00 white silk takes a firm bite of the sclera at the site of the first cautery mark at 10 mm. from the limbus at the lateral border of the inferior rectus and with a very sharp ground-down Graefe knife the resection is started here. This is the only difficult part of the operation for once the desired depth is reached—and this should be such that a film of the deepest scleral lamellæ of tissue paper thickness intervenes between the knife and the suprachoroidal space—it is quite easy to continue in this plane and indeed to vary the thickness of the sclera resected as desired. At about every 2·5 mm. of resection a single suture of 00 white silk on a Maddox needle is inserted and for this operation I have found it better not to use mattress sutures which tend to break on tying. When the resection is completed the exposed surface of the choroid covered with its very thin film of the deepest scleral lamellæ is touched along its whole length with an orange stick which has been dipped in 3% caustic potash. Before tying off the scleral sutures it is important to lower the intra-ocular tension by two or three katholysis needle punctures (2 milliamps.) through the site of resection. The external rectus is re-attached to its stump of insertion and the conjunctiva and Tenon's capsule sewn up with interrupted sutures of No. 0 black silk. The length of the scleral strip removed averages 30 mm.

The advantages of this operation over the full thickness resection of the sclera are : little or no danger of vitreous loss especially when passing through an area previously diathermized, no bulging of the exposed choroid and no need to reduce the intra-ocular tension until the resection is completed.

Whether the operation is as efficacious as a full thickness resection I do not know as the numbers are, as yet, much too small to form any reasoned opinion. To date one aphakic has been cured and three appreciably improved. Two high myopes have also been improved, the rest have been failures. However, as all but one of these cases had been total failures by the diathermy operation it would appear that scleral resection is well worth trying especially in aphakics in whom no retinal defect can be found. In these cases I am now trying this operation as the primary operative procedure and I think it should be so undertaken for myopes with thin atrophic retinæ and especially for cases with multiple and widely separated tears in front of the equator of the globe.

REFERENCES

Lancet Editorial (1929), ii, 1202.
SHAPLAND, C. DEE (1948) *Trans. Ophthal. Soc. U.K.*, **68**, 115.

Dr. Jacques Rougier (Lyons) said that the discussion on the treatment of retinal detachment had been very interesting. In Lyons they had been employing these scleral resections for about two months and so far they had treated about 20 cases. They had the same point of view on the indications for scleral resection in aphakia, myopia, and old detachment as had been advanced by the speakers, and this seemed to be the only operation which could give any chance of cure in those cases. He had been particularly interested in Mr. Shapland's communication because in Lyons they were following exactly the same technical procedure. They used a lamellar scleral resection, and it seemed that the lamellar resection was sufficient to give a good retraction of the sclera.

One thing which disturbed him was the question of the hole or tear and he would like to have his mind clear on the point. They had found a number of cases of retinal detachment on the site of the tear, and now they always combined scleral resection with some diathermy points around the tear. He was sorry he could not give the results because it was only two months since this procedure was started. The results had so far been encouraging, but when the patient had had one, two or three diathermy operations the result was not so good or was even quite unsuccessful. When the pressure was very high they were accustomed to puncture the anterior chamber and so make the eye softer, and thus, it was easier to tie up the scleral stitches.

Mr. Lister, in reply, said that there were one or two points on which he differed from Mr. Philps. He always painted the choroid with 3% potash. Again, he thought that one should certainly close the hole. To leave the hole open behind the resection would be to ask for trouble.

Concerning paracentesis, he had made a practice of carrying this out before starting the resection in order to diminish the bulging of the choroid which was apt to make stitching up difficult. He had, however, modified his views since a case of aphakic detachment, which had responded most successfully, had later developed a shallow detachment localized to the macular area. This appeared to be due to attachment of the vitreous to the paracentesis incision and it was probably wise, therefore, to avoid paracentesis in aphakic cases.

In reply to a question as to whether he neutralized the potash, he said that he did not; this was not really needed in the weak dilutions employed.

Mr. Philps said, in answer to Mr. King's question as to whether he used scleral resection in an aphakic detachment where he found a hole, that he had not done so for the simple reason that he had not had an aphakic detachment in which he had a hole. The scleral resection readjusted in some way the mechanics of an aphakic eye and he did the scleral resection in preference to a diathermy operation.

In answer to Dr. Rougier, he thought it was important where the scleral resection was placed and it should be over the hole, but the trouble was that very often no hole was found and one was confronted with a complete detachment of the lower half of the retina of long standing and there was no good indication whether the hole lay in the lower half of the retina or elsewhere and the fluid had run downwards. It had to be remembered that the greater number of retinal holes lay on the temporal part rather than on the nasal part of the eye. Therefore if in doubt the best procedure was to do a resection of the outer half of the globe pursuing it to at least 6 or 7 o'clock. That was where the greater number of retinal holes occurred.

As to what period should elapse after diathermy before one did a resection, the answer was the longer the better; it depended very much upon whether the detachment was superior or inferior. If it was superior then one could not wait. The patient had to be left lying in bed and might easily grow impatient, and one must get on with it. On the other hand, if the detachment was inferior, then it was often a good thing to get the patient up and walking about before going on with the operation.

He had tried chemical cauterization in only one case. This was the patient described who had a total vitreous hæmorrhage three days after operation. Obviously there was no connexion between the chemical cauterization and the vitreous hæmorrhage.

Mr. Dee Shapland, in reply, said that he had been asked what happened to the film of scleral tissue left at operation. This, he said, was a little difficult to answer, but after the operation one could see in the fundus a ridge running just behind and concentric with the ora serrata, and he imagined that the very thin lamina of the deepest scleral fibres followed the movements of the choroid and pleated in with this membrane.